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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. METABOLIC STUDY OF 7-METHYLBENZO[A]PYRENE WITH RAT LIVER MICROSOMES: SEPARATION BY REVERSED-PHASE AND NORMAL-PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY AND CHARACTERIZATION OF METABOLITES.

Wong TK, Chiu PL, Yang SK
Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014
Chem Biol Interact; 36(2):153-166 1981

The 7-methylbenzo[a]pyrene (7-MBaP) was incubated with liver microsomes of rats pretreated with polychlorinated biphenyls (Aroclor 1254) (PCBs). Metabolites of 7-MBaP were isolated by both reversed-phase and normal-phase high performance liquid chromatography (HPLC) and were characterized by nuclear magnetic resonance, UV-visible and mass spectral analyses. The predominant metabolite of 7-MBaP was found to be 3-hydroxy-7-methylbenzo[a]pyrene (3-hydroxy-7-MBaP). Other identified metabolites include 7-MBaP 4,5-, 7,8- and 9,10-trans-dihydrodiols, 7-hydroxymethyl-BaP, 7-hydroxymethyl-BaP trans-9,10-dihydrodiol, 9-hydroxy-7-MBaP 3-hydroxy-7-hydroxymethyl-BaP, 7-MBaP 1,6-and 3,6-quinones and a hydroxyquinone which is also formed by further metabolism of the 3-hydroxy-7-MBaP. Comparative metabolic studies of 7-MBaP and BaP indicated that, relative to that of BaP, the methyl substituent of 7-MBaP slightly increases the formation of 3-hydroxy-7-MBaP and decreases the metabolism at other regions of the 7-MBaP molecule. The finding that a 7,8-dihydrodiol is a metabolite indicates that, like BaP, 7-MBaP may also be activated to the potentially reactive 7,8-dihydrodiol 9,10-epoxides although their formations are significantly reduced. (Author abstract) (22 Refs)

2. METABOLIC FATE AND CARCINOGENICITY OF N-(OMEGA-HYDROXYALKYL)-N-(4 HYDROXYBUTYL)NITROSAMINES, ANALOGS OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE, IN THE RAT.

Suzuki E, Takeda Y, Mochizuki M, Hashimoto Y, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):539-546 1981

The metabolic fate and carcinogenicity of three omega-hydroxy derivatives of N-alkyl-N-(4-hydroxybutyl)nitrosamines, potent bladder carcinogens, were investigated in the rat. They were N-(2-hydroxyethyl)-N-(4-hydroxybutyl)nitrosamine (HEHBN), N-(3-hydroxypropyl)-N-(4-hydroxybutyl)nitrosamine (HPHBN), and N,N-bis(4-hydroxybutyl)nitrosamine (BHBN). The principal urinary metabolite of HEHBN as well as HPHBN was identified as the corresponding 3-carboxypropyl compound, while the main metabolite of BHBN was N,N-bis(3-carboxypropyl)nitrosamine, indicating the preferential metabolic oxidation of the 4-hydroxybutyl chain to the 3-carboxypropyl group in the N-(omega-hydroxyalkyl)-N-(4-hydroxybutyl)nitrosamines. All three N-nitrosamines having the 4-hydroxybutyl chain induced neither bladder tumor nor any tumor in other organs under conditions similar to those used for N-alkyl-N-(4-hydroxybutyl)nitrosamines. The essential structural and metabolic requirements in N-nitrosamines for the induction of bladder cancer in the rat are discussed. (Author abstract) (25 Refs)

3. METABOLIC FATE OF N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE AND N,N-DIBUTYLNITROSAMINE IN THE GUINEA PIG, WITH REFERENCE TO THEIR CARCINOGENIC EFFECTS ON THE URINARY BLADDER.

Suzuki E, Aoki J, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(4):547-551 1981

The metabolic fate of two urinary bladder carcinogens, N-butyl-N-(4-hydroxybutyl)nitrosamine(BBN) and N,N-dibutylnitrosamine (DBN), was studied in the guinea pig, in order to elucidate species differences of response to these N-nitrosamines in this animal species and the rat. Based on the urinary metabolites characterized after oral administration of these compounds, the metabolic pathways of BBN and DBN in the guinea pig were shown to be essentially similar to those in the rat. The principal urinary metabolite of BBN and DBN in the guinea pig, however, was not N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN), as was the case in the rat, but the glucuronic acid conjugate of BBN and that of N-butyl-N-(3-hydroxybutyl)nitrosamine, respectively. The species variation in response to BBN and DBN as bladder carcinogens in these animals is discussed on the basis of the urinary excretion of BCPN. (Author abstract) (27 Refs)

4. SALIVARY LEVELS OF N-NITROSAMINES AND SOME METABOLITES AFTER IP INJECTION OF N-NITROSAMINES IN RATS.

Fliessbach JH, Guttenplan JB
Dept. Biochemistry, New York Univ. Dental Center, New York, NY, 10010
Res Commun Chem Pathol Pharmacol; 33(2):283-291 1981

The carcinogens N-nitrosodimethylamine (DMN) and N-nitrosodiethylamine (DEN) were detected in rat saliva by gas liquid chromatography or HPLC after their ip injections. Salivary levels were equal to or greater than blood levels. A fairly linear dose response in salivary levels was observed in the range of 1-50 mg/kg. Salivary levels of DMN and DEN decreased between 0.5 and 1.0 hr after administration with the decrease becoming more prominent at lower doses. Formaldehyde and bicarbonate, metabolites of DMN, were also detected in rat saliva. (Author abstract) (19 Refs)

5. MASS SPECTROMETRY OF 2-SUBSTITUTED 5-NITRO-2-FURYL THIAZOLES. IDENTIFICATION OF MICROSOMAL NITROREDUCTION PRODUCTS BY ELECTRON IMPACT MASS SPECTROMETRY.

Mattammal MB, Zenser TV, Davis BB
St. Louis Veterans Admin. Medical Center, Geratric Res., Education and Clinical Center, St. Louis, MO, 63125
Biomed Mass Spectrom; 8(7):305-311 1981

The electron impact mass spectral fragmentation of nitro heterocyclic carcinogens N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, 2-amino-4-(5-nitro-2-furyl)thiazole, 2-methyl-4-(5-nitro-2-furyl)thiazole and 2-methylamino-4-(5-nitro-2-furyl)thiazole were studied. The molecular ions undergo two modes of cleavage: one giving [M-84]+ ions which include the 2-substituted thiazole ring, while the other gives rise to the fragment [M-74]+ ions. The products of anaerobic microsomal nitroreduction of 2-methyl-4-(5-nitro-2-furyl)thiazole were isolated and purified by high-pressure liquid chromatography. The metabolites undergo different fragmentation patterns com-

pared to the parent nitro analogs. Metabolites from anaerobic enzymatic reduction showed identical gas chromatographic, high-pressure liquid chromatographic and thin-layer chromatographic properties to the chemically synthesized material. The metabolites were identified as 1-(2-methyl-4-thiazolyl)-3-cyano-1-propenone and 1-(2-methyl-4-thiazolyl)-3-cyano-1-propanone by mass spectral fragmentation pattern. (Author abstract) (22 Refs)

6. CHLOROETHANES: THEIR METABOLISM BY HEPATIC CYTOCHROME P-450 IN VITRO.

Ivanetich KM, Van Den Honert
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory 7925 Cape, South Africa
Carcinogenesis; 2(8):697-702 1981

Hepatic Microsomes were obtained from male Long-Evans rats. Microsome suspensions were exposed to 1,1,1-trichloroethane (111T), 1,1,2-trichloroethane (112T), or 1,1,2,2-tetrachloroethane (1122T). Levels of cytochrome P450 were measured, and metabolites of the chloroethanes were identified and quantified. The binding of chloroethanes was enhanced by the induction of cytochrome P-450 by phenobarbital (PB). It was not enhanced by the induction of cytochrome P-448 by beta-naphthoflavone (BNF). All three chloroethanes stimulated CO-inhibitable NADPH oxidation (CINO) by the hepatic microsomes. BNF induction decreased CINO for all three chloroethanes. PB induction increased CINO for 111T and 112T, but not for 1122T. CINO and metabolite formation were inhibited by CO, 2-diethylaminoethyl-2,2-diphenylvalerate (SKF-525A), and/or metyrapone. The results confirmed that all three chloroethanes were metabolized by cytochrome P-450. The metabolites of 111T, 112T, and 1122T were 2,2,2-trichloroethanol, monochloroacetate, and dichloroacetate, respectively. Proposed mechanisms for metabolism are described, with relationship to the relative mutagenicity and carcinogenicity of the three chloroethanes. (29 Refs)

OTHER METABOLISM OF CARCINOGENS

7. RELEASE OF MUTAGENIC METABOLITES OF BENZO[A]PYRENE FROM THE PERFUSED RAT LIVER AFTER INHIBITION OF GLUCURONIDATION AND SULFATION BY SALICYLAMIDE.

Bock KW, Bock-Hennig BS, Lilienblum W, Volp RF
Dept. Pharmacology and Toxicology, Univ. Gottingen, Kreuzbergring 57, D-3400 Gottingen, W. Germany
Chem Biol Interact; 36(2):167-177 1981

The role of glucuronide and sulfate conjugation in presystemic inactivation of benzo[a]pyrene (BP) metabolites was investigated with rat livers perfused with BP (12 u moles). Comparisons were made between metabolite profiles and mutagenicity of medium from perfusions with and without salicyclamide, a selective inhibitor of glucuronide and sulfate conjugation. After 4 hr perfusion in the presence of salicylamide, certain BP metabolites (diols, quinones, phenols, and metabolites more polar than BP-9,10-diol) were significantly increased at the expense of quinones and phenols in the glucuronid e fraction. Mutagenicity of medium (detected by the Ames test, using tester strains TA98 and TA100) was low in perfusion without salicylamide. Mutagenicity detected with tester strain TA98 was significantly increased in perfusions with salicylamide. Involvement of glucuronidation in BP inactivation was also observed at the subcellular level when cofactors of glucuronidation were added to liver homogenates along with the NADPH regenerating system in the Ames test, BP mutagenicity was markedly decreased. Both the activation of BP to mutagenic metabolites and the inactivation of BP metabolites by glucuronidation was much more pronounced with liver homogenates from 3-methyl-cholanthrene-treated rats than with those from phenobarbital-treated animals or untreated controls. The results suggest an important role for glucuronidation and sulfation in the inactivation and elimination of polycyclic aromatic hydrocarbons. (Author abstract) (26 Refs)

8. GLUCURONIC ACID CONJUGATES OF METABOLITES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE EXCRETED THROUGH BILE DUCTS IN RAT.

Khanduja KL, Dogra SC, Sharma RR
Dept. Biophysics, Postgraduate Inst. Medical Education and Res., Chandigarh 160 012, India
Indian J Exp Biol; 19(4):375-378 1981

The nature of metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) excreted through the biliary ducts of female Wistar rats was examined through thin layer and column chromatography. The results indicated that diols or dihydrodiols and not phenols of DMBA could be the main metabolites which conjugate with glucuronic acid for rapid excretion of the carcinogen in the bile. (24 Refs)

9. METABOLIC FATE OF N,N-DIPROPYLNITROSAMINE AND N,N-DIAMYLNITROSAMINE IN THE RAT, IN RELATION TO THEIR LACK OF CARCINOGENIC EFFECT ON THE URINARY BLADDER.

Suzuki E, Okada M
Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(6):552-561 1981

The metabolic fate of N,N-dipropylnitrosamine (DPN) and N,N-dipentyl(=diamyl)nitrosamine (DAN), which induce tumors principally in the liver and esophagus but not in the urinary bladder, was studied in the rat, in order to elucidate the reason for this lack of carcinogenicity to the urinary bladder in contrast with the butyl homolog, N,N-dibutylnitrosamine (DBN), a potent bladder carcinogen. The principal urinary metabolite of DPN was identified as the omega-oxidation product N-propyl-N-(2-carboxyethyl)nitrosamine. The (omega-1)-oxidation product N-propyl-N-(2-hydroxypropyl)nitrosamine and its glucuronic acid conjugate were also characterized as metabolites. The principal urinary metabolite of DAN was N-amyl-N-(2-carboxyethyl)nitrosamine, which was formed by metabolic shortening of the amyl chain by omega- and beta-oxidations according to the Knoop mechanism. Besides this, seven compounds oxidized at omega-, (omega-1)-, (omega-2)-, and (omega-3)-positions of one or both amyl chains were isolated and characterized, some of which were shown to be also present as the corresponding glucuronide. The metabolic pattern of DPN and DAN was compared with that of DBN, and the lack of carcinogenicity of the former N-nitrosamines to the urinary bladder of rats is discussed on the basis of their urinary metabolites. (Author abstract) (20 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

10. THE IMPORTANCE OF SHORT TERM EXPOSURE OF C3H 10T1/2 CELLS TO POLYCYCLIC HYDROCARBONS: EVIDENCE FOR HYDROCARBON-MEDIATED ANTICARCINOGENIC ACTIVITY.

Sarrif AM, Strobel-Stevens J, Miller C, Smythies JR
Dept. Pharmacology, Univ. Alabama in Birmingham Medical Center, Birmingham, AL, 35255
Cancer Lett; 13(4):291-297 1981

The effects of short term exposure of C3H 10T1/2 mouse embryo cells to benzo[a]pyrene (BP) and 3-methylcholanthrene (3-MC) were studied. Within the concentration range of 0.3 to 10 ug/ml, increasing the time of exposure from 15 min to 24 hr did not alter cytotoxicity (as determined by plating efficiency) appreciably; cell survival ranged between 70-90% of control. For both carcinogens, transformed foci were observed in as little as 15 min. Between 0.3-1.25 ug/ml BP, transformation frequency (TF) (the number of transformed foci/1,000 surviving cells) increased with time of exposure; at concentrations between 2.5-10 ug/ml a max TF of 2 was observed for cells exposed to BP for 3 hr. Exposure to high concentrations of 3-MC produced an optimal TF after 30 min to 1 hr. The dependency of TF on BP or 3-MC concentration at selected times was profiled. One hr exposure produced a TF which increased with increasing concentrations. After BP exposure for 3 hr, TF reached a max of 2 at 5 ug/ml; after 6 hr TF peaked at 1.25 ug/ml and decreased at higher concentrations. Results with 3-MC differed: with a 3 hr incubation TF peaked at 1.25 ug/ml and at 24 hr 0.625 ug/ml caused max TF. The changes observed in TF were not likely to result from toxic effects. In this study the transformation of 10T1/2 cells by BP and 3-MC depended upon both concentration and time of exposure. Since both BP and 3-MC are extensively metabolized to polyoxygenated derivatives and conjugates, certain of the metabolites may have acted as antipromoting agents. (21 Refs)

11. EFFECT OF GLUTATHIONE AND URIDINE 5'-DIPHOSPHOGLUCURONIC ACID ON MUTAGENESIS BY BENZO[A]PYRENE AND AFLATOXIN B1 IN THE SALMONELLA/MICROSOME ASSAY.

Malaveille C, Brun G, Hautefeuille A, Bartsch H
Programme of Environmental Carcinogens and Host Factors, Div. Chemical and Biological Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert-Thomas, F-69372 Lyon Cedex 2, France
Mutat Res; 83(1):15-24 1981

The role of the conjugating enzymes, glutathione-S-transferase (GSH-S-T) and uridine 5'-diphosphoglucuronic acid (UDPGA) on rat liver S9-mediated mutagenesis of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in the Salmonella/microsome assay was investigated. In S typhimurium TA100, the UDPGA-dependent reduction of BP mutagenicity was related to the liver S9 concentration: max reduction (40%) in mutagenicity was noted with an S9 concentration of 50 ul/plate. In liquid assays, the presence of 2.5 milliM UDPGA for 20 min caused a two-fold increase in BP mutagenicity at a concentration of 40 uM BP. At 20 uM BP, the presence of UDPGA either did not change or decreased mutagenicity of BP; after 30 min of incubation, a significant decrease was observed. With 20 and 40 uM BP, the addition of GSH to the assays decreased BP mutagenesis by 1.8-and 1.5-fold in the presence of 17% and 9% (vol/vol) liver S9, respectively. GSH had no effect at two-fold lower concentrations of BP. The effect of glutathione (GSH) on AFB mutagenesis was dependent on its concentration. AFB mutagenicity decreased at concentrations of AFB greater than 7.5 nanoM; at 30 nanoM AFB, the AFB mutagenesis was reduced by 1.8-fold. In liquid assays, in the presence of 4.4% S9 from untreated rats the addition of 10 milliM GSH changed the AFB mutagenesis only at concentrations greater than 100 nanoM, resulting in an enhancement of AFB mutagenicity. (43 Refs)

12. PROMOTIVE EFFECTS OF DEOXYCHOLIC ACID ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE IN MALE RATS.

Cameron R, Imaida K, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 72(4):635-636 1981

The ability of deoxycholic acid (DA), administered over a short time period, to promote the appearance of hyperplastic foci or hyperplastic nodules in diethylnitrosamine (DEN)-initiated male Fischer rats was examined. The 80 rats were divided into five groups, 15 rats in Groups 1-4 and 20 rats in Group 5. Groups 1, 3, and 5 were injected ip with DEN and later Groups 1 and 3 were fed 0.5% DA or 0.05% phenobarbital (PB), respectively, for 10 wk. Groups 2 and 4 were given saline in place of DEN and later fed DA or PB alone for 10 wk. Both DA and PB (Groups 1 and 3) promoted the development of considerable numbers of foci positive for gamma-glutamyl transferase if preceded by DEN initiation. DEN alone (Group 5) induced much fewer and relatively small foci but induced no hyperplastic nodules. Significantly more and larger foci and a considerably greater number of hyperplastic nodules were seen with DA (Group 1) than with PB (Group 3). DA without DEN (Group 2) induced a small number of foci and hyperplastic nodules. These data suggested that DA is a moderately strong promoter of preneoplastic liver lesions in the male rat. (9 Refs)

13. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE D IET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

Kiessling M, Lipinski R, Bohm N, Kleihues P
Pathologische Institut, Universitat Freiburg, 78 Freiburg, W. Germany
Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity

of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

14. EFFECTS OF HARMAN AND NORHARMAN ON THE METABOLISM OF ANILINE AND P-DIMETHYLAMINOAZOBENZENE.

Hayashi K
Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan
Nippon Eiseigaku Zasshi; 36(2):495-505 1981

The metabolism and mutagenicity of aniline and p-dimethylaminoazobenzene (p-DAB) were studied in vitro using rat liver microsomes. In the absence of harman (l-methyl-9H-pyrido[3,4-b]indole) and norharman (9H-pyrido[3,4-b]indole), p-DAB was metabolized to aniline without accumulation of p-methylaminoazobenzene (p-MAB) or p-aminoazobenzene (p-AAB). Aniline was metabolized to p-aminophenol (p-AP). Harman or norharman substantially inhibited metabolism of aniline to p-AP in microsomes. Norharman was a greater inhibitor than harman. Norharman slightly reduced the metabolism of p-DAB to aniline and caused the accumulation of p-DAB, p-MAB, and p-AAB. The metabolites of aniline, o-aminophenol, m-aminophenol, p-AP, and nitrosobenzene, were tested for mutagenicity in Salmonella typhimurium TA98. Nitrosobenzene was mutagenic only in the presence of norharman with S-9 mix. Similarly p-MAB, p-AAB, and aniline were mutagenic in TA 98 only in the presence of norharman with S-9 mix. Harman and norharman each greatly inhibited aniline hydroxylase activity, while aminopyrene demethylase had only a slight effect. Aryl hydrocarbon hydroxylase was inhibited by norharman, but not by harman. (23 Refs) (In JPN)

15. NITRITE CONVERTS 2-AMINO-ALPHA-CARBOLINE, AN INDIRECT MUTAGEN, INTO 2-HYDROXY-ALPHA-CARBOLINE, A NON-MUTAGEN, AND 2-HYDROXY-3-NITROSO-ALPHA-CARBOLINE, A DIRECT MUTAGEN.

Tsuda M, Nagao M, Hirayama T, Sugimura T
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Mutat Res; 83(1):61-68 1981

The conversion of 2-amino-alpha-carboline (AAC), a mutagen isolated from the pyrolysate of soybean globulin, into a non-mutagenic hydroxy derivative and then into a new mutagen by treatment with nitrite under acidic conditions is reported. AAC was mutagenic to Salmonella typhimurium in the presence of a rat-liver microsomal fraction (S9 mix). 25 nanomoles of AAC induced 1,156 and 108 revertants of TA98 and TA100, respectively, with S9 mix, and no revertants without S9 mix. Incubation with nitrite under acidic conditions decreased or abolished the mutagenicity with S9 mix. However, below pH 3, mutagenicity that did not require S9 mix appeared. This direct acting mutagen was found to be 2-hydroxy-3-nitroso-alpha-carboline (HNAC) by mass and proton magnetic resonance spectroscopy. It was shown that AAC was converted into 2-hydroxy-alpha-carboline which was then converted into HNAC. The physiological significance of these findings are discussed. (30 Refs)

16. MODIFICATION OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RATS WITH INDUCERS OF THE CYTOCHROMES P-450.

Hales BF
Dept. Pharmacology and Therapeutics, McGill Univ., Montreal, Quebec H3G 1Y6, Canada
Teratology; 24(1):1-11 1981

The chemotherapeutic agent cyclophosphamide (CP) may act as a carcinogen if it is enzymatically metabolized to reactive intermediates with alkylating, mutagenic, or cytotoxic effects, which activation is thought to be catalyzed by the cytochrome P-450 monooxygenase system. Phenobarbital (PB) induces the hepatic cytochrome P-450 that is involved in the activation of CP to both alkylating and mutagenic metabolites; beta-naphthoflavone (bNF) induces a different cytochrome P-450 and actually decreases the activation of CP by liver microsomes. Using rats pretreated with either PB or bNF, the activation of CP to mutagenic metabolites by enzyme fractions on day 13 of gestation was measured with the Ames test on Salmonella typhimurium TA1535 and teratogenicity was assessed in vivo by treatment of rats with CP on day 13 of gestation. CP was activated to mutagenic metabolites to the same extent (on a tissue wet wt basis) by enzyme fractions from maternal liver, kidney, and placenta, despite differences in cytochrome P-450 content, but fetal homogenates did not activate CP. PB pretreatment increased the liver cytochrome P-450 content 1.8-fold and the activation of CP by maternal liver microsomes 10-fold; however, PB did not alter the activation of CP by maternal kidney, by placenta, or by the fetus. PB pretreatment increased the teratogenicity of CP as measured by an increased incidence of malformed embryos or by decreased fetal wt. Pretreatment with bNF did not induce the hepatic cytochrome P-450 in the pregnant rat; did not change the activation of CP to mutagenic metabolites by liver, kidney, the placenta, or the fetus; and had no effect or decreased the teratogenicity of CP. These results suggest that the mother, rather than the fetus, is the site of PB activation; that the principal site of activation is the maternal liver; and that there is a correlation between the teratogenicity and mutagenicity of CP after induction by cytochrome P-450. (36 Refs)

17. EFFECTS OF 2-AND 3-TERT-BUTYL-4-HYDROXYANISOLE ON GLUTATHIONE S-TRANSFERASE AND EPOXIDE HYDROLASE ACTIVITIES AND SULFHYDRYL LEVELS IN LIVER AND FORESTOMACH OF MICE.

Lam LK, Sparnins VL, Hochalter JB, Wattenberg LW
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Cancer Res; 41(10):3940-3943 1981

Butylated hydroxyanisole, a food additive, has been found to inhibit the neoplastic effects of a wide variety of chemical carcinogens. The commercially available preparations of butylated hydroxyanisole contain two isomers, 2-tert-butyl-4-hydroxyanisole (2-BHA) and 3-tert-butyl-4-hydroxyanisole (3-BHA). Both isomers induce increased activities of glutathione (GSH) S-transferase and epoxide hydrolase and increase acid-soluble sulfhydryl concentration in hepatic and forestomach tissues of A/HeJ mice. The inductions were assayed after 2 wk of feeding diets containing the two isomers. 3-BHA induced an increase in the activity of hepatic microsomal epoxide hydrolase by 1.4x that of the control. The activity of cytosol GSH S-transferase was enhanced by both isomers. In the liver, the 3-BHA induction was more than 3x higher than that of 2-BHA. In the forestomach, however, the induction effect of the two

isomers was reversed. The overall magnitude of the induction was much lower in the forestomach than in the liver. Synergistic effects on the induction of GSH S-transferase activity were observed in the forestomach cytosol when mixtures of different proportions of the two isomers were added to the diet. Max enzyme activity was obtained at a ratio of 75% 2-BHA and 25% 3-BHA. No synergistic effect was observed with the corresponding hepatic cytosolic enzyme. The relative inductive effects of 2-and 3-BHA on the acid-soluble sulfhydryl level of liver and forestomach tissues followed closely those on GSH S-transferase activity. The results of the present study show that the two isomers of butylated hydroxyanisole differ in the magnitude of their effects on carcinogen-metabolizing systems of the liver and forestomach. (Author abstract) (27 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

18. FRAMESHIFT MUTATIONS: RELATIVE ROLES OF SIMPLE INTERCALATION AND OF ADDUCT FORMATION.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):21-30 1981

The mutagenic properties of 9-aminoacridine, its derivative quinacrine, and the nitro-containing derivative Entozon were examined in Salmonella typhimurium and Escherichia coli WP2uvrA assays. Both 9-aminoacridine and quinacrine induced frameshift mutations in strain TA1537 only (with, respectively, 1.7 and 3.0 revertants/nanomole (r/nm)), confirming the finding that simple intercalators mutate this strain alone. Entozon primarily affected strains TA98 (338 r/nm) and TA1538 (288 r/nm), indicators for frameshift mutations resulting from adduct formation; mutagenicity was greatly decreased when Entozon was tested in strain TA1978 (23 r/nm), the uvrB+ analog of TA1538 which does not respond maximally to the mutagenic action of adduct-forming chemicals as a result of its intact uvrB system. Entozon displayed no base-substitution activity for Salmonella, although it exhibited some activity when tested in E coli WP2uvrA (2.4 r/nm). When a cell is exposed to a molecule inducing frameshift mutations by intercalation and adduct formation, the formation of adducts apparently exerts a much stronger influence on total mutagenic expression. (47 Refs)

19. RAT HEPATOCYTE-MEDIATED MUTAGENESIS OF HUMAN CELLS BY CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS BUT NOT ORGANOCHLORINE PESTICIDES.

Tong C, Fazio M, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 167(4):572-575 1981

The establishment of a hepatocyte primary culture-mediated human cell hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutagenesis assay is reported. In the rat hepatocyte primary cultures (HPC)-mediated Detroit 550 (D-550) HGPRT mutation assay, 1 x 10(6) D-550 were generally coplated with 20 x 10(6) freshly prepared HPC. The cocultures were allowed to attach for 2 hr, were washed, and fresh media containing the carcinogens or appropriate controls were added for 24 hr exposure. The cultures were washed then allowed to grow for 10 days to allow mutant expression. In general, by day 4, no viable HPC were observed. HGPRT mutants were selected in the human foreskin cell line D-550 by 6-thioguanine (TG). Exposure of D-550 alone to benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene did not result in any increase in TG-resistant (TGr) mutant incidence over the parallel-run control. However, a significant increase in the TGr mutant incidence over that in control cultures occurred in D-550 when the carcinogen exposure was in the presence of HPC. With dichlorodiphenyltrichloroethane, chlordane, and mirex, no significant increase in TGr mutant incidence was observed in the exposed human cells either in the presence or absence of HPC. An epigenetic mechanism for the carcinogenicity of these organochlorine pesticides is suggested. (34 Refs)

20. NITRATED FLUORENE DERIVATIVES ARE POTENT FRAMESHIFT MUTAGENS.

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Mutat Res; 90(1):11-20 1981

The structure-activity relationship of polynitrated polycyclic aromatic hydrocarbons (PAH) which might be present in the environment as a result of incomplete combustion and subsequent nitration by oxides of nitrogen was investigated. The biological activity of 2-nitrofluorene, 2,7-dinitrofluorene, 2,7-diaminofluorene, (2,4,7-trinitro-9-fluorenylidene) malononitrile, 2,4,5,7-tetranitro-9-fluorenone, 2,7-dinitro-9-fluorenone, and 2,4,7-trinitro-9-fluorenone was studied. Significant mutagenic activity was observed for all the compounds in Salmonella typhimurium strains TA1538, TA98, and TA1537; a corresponding lack of activity or only minimal activity was observed in strain TA1535 and in Escherichia coli WP2 uvrA, indicating a frameshift type of mutagenicity. Mutagenic action is based on a reduction of the nitro-function to the corresponding hydroxylamines, the penultimate mutagens, which following esterification to electrophiles apparently react with the guanine moiety of DNA to form adducts. Max mutagenic activity was observed with the trinitro-substituted compound; addition of a fourth nitro group resulted in diminished activity, presumably reflecting steric hindrance of either enzyme reduction of the nitro-function or of DNA-adduct formation. (45 Refs)

21. MUTAGENICITY OF N-ALKYL-N-(ALPHA-ACETOXYALKYL)NITROSAMINES IN V79 CHINESE HAMSTER CELLS IN RELATION TO ALKYLATING ACTIVITY.

Huang GF, Mochizuki M, Anjo T, Okada M
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Gan; 72(4):531-538 1981

Mutation to ouabain resistance and cytotoxicity were tested in V79 Chinese hamster cells after the cells had been treated for 2.5 hr with a series of N,N-dialkylnitrosamines (alkyl=methyl, ethyl, propyl, butyl or tert-butyl) monosubstituted at the alpha-carbon with an acetoxy group. The effects of the length of alkyl chain and the mode of substitution with the acetoxy group on the cytoxicity and mutagenicity were examined. In the series of N-alkyl-N-(acetoxymethyl)nitrosamines with an acetoxy group at the primary alpha-carbon, the methylating compound N-methyl-N-(acetoxymethyl)nitrosamine was the most cytotoxic and mutagenic, and the biological activities decreased in the order of ethyl, butyl and propyl homologs. N-

tert-Butyl-N-(acetoxymethyl)nitrosamine was not mutagenic at the concentration tested. At equitoxic concentration, N-ethyl-N-(acetoxymethyl)nitrosamine was found to be the most mutagenic. Of the two N-alkyl-N-(alpha-acetoxybutyl)nitrosamines having an acetoxy group at the secondary alpha-carbon, N-methyl-N-(alpha-acetoxybutyl)nitrosamine was more cytotoxic and mutagenic than N-butyl-N-(alpha-acetoxybutyl)nitrosamine. A comparison of the corresponding N-alkyl-N-(acetoxymethyl)nitrosamines and N-alkyl-N-(alpha-acetoxybutyl)nitrosamines showed that the latter had stronger activities. A plot of the mutation frequency versus the ability of the alpha-acetoxy compounds to alkylate 4-(p-nitrobenzyl)pyridine was linear. This indicates that the chemical reactivity of the compounds plays an important role in inducing mutation in V79 Chinese hamster cells. (Author abstract) (26 Refs)

22. MUTAGENICITY OF REACTION PRODUCTS OF SULPYRINE WITH NITRITE.

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Mutat Res; 90(1):57-65 1981

The mutagenicity of three N-nitroso products of sulpyrine (1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide hydrate (DPMN), 4-(N-methyl-N-nitroso)aminoantipyrine (MNAA), and 1-acetyl-1-methyl-2-nitroso-2-phenylhydrazine) and of related compounds (4-methylaminoantipyrine, 1-acetyl-1-methyl-2-phenylhydrazine, 4-hydroxyantipyrine, sulpyrine, and sodium nitrite) was tested on Salmonella typhimurium TA100 and TA98. DPMN, MNAA, and sodium nitrite were mutagenic to TA100 but not to TA98. None of the other compounds were mutagenic to either strain. Activation of mutagenicity with rat-liver microsomal preparation (S9 mix) was required by MNAA, but not by DPMN. The addition of L-cysteine or glutathione markedly increased the mutagenicity of DPMN; the enhancing effects were proportional to concentration added. The possibility that sulpyrine might pose a carcinogenic hazard in man is discussed. (25 Refs)

23. MUTAGENICITY OF AMIDE TYPE AND CARBAMATE TYPE DIAZOALKANE-GENERATING AGENTS IN SALMONELLA/MICROSOME ASSAY.

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Chem Pharm Bull (Tokyo); 29(6):1758-1762 1981

Both amide type and carbamate type N-nitroso compounds, which have a common structure and have been reported to be excellent diazoalkane-generating compounds were examined for mutagenicity by measuring their ability to create histidine (his) prototrophic revertants of two his-dependent Salmonella typhimurium strains: T100 (a base-pair substitution strain) and TA98 (a frameshift strain), with and without metabolic activation by S-9 mix. Six compounds of each type having systematic substitutions at two different sites of the basic common structure were examined systematically over dose ranges of 0.27-2.7 umole (4 x 10(-5) to 4 x 10(-2) M). In the absence of activation, none of the amide type compounds showed any mutagenicity in either strain. With metabolic activation, two of six amide type compounds (both having a benzyl group in the same position) were weakly mutagenic to TA100. In the absence of S-9 mix, only one of six carbamate type compounds showed any mutagenicity (against TA98); in the presence of S-9 mix, all six carbamate compounds were mutagenic against TA100 over a wide range of concentrations and two of six were weakly mutagenic against TA98. There is apparently a structure-mutagenicity relationship for amide type and carbamate type compounds that is principally dependent upon the rate of chemical generation of diazoalkane or phenyldiazomethane in alkaline soln. (8 Refs)

24. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

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JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutagenic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved . (Author abstract) (31 Refs)

25. FRAMESHIFT MUTAGENESIS OF 9-AMINOACRIDINE DERIVATIVES IN SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(1):1-10 1981

A number of 9-aminoacridine derivatives with various substituents on the exocyclic amino group were tested in the absence of activation by rat-liver microsomes in order to determine the effect of the substituents on frameshift activity and specificity. The four acridine derivatives tested were 9-aminoacridine, a spin-labeled 9-aminoacridine derivative (4-(9-acridinylamino)-2,2,6,6-tetramethyl-1 piperidinyloxy), quinacrine dihydrochloride, and the putative bisintercalator N,N'-bis(2-methoxy-6-chloroacridine)-tetraethyl enephetamine pentahydrochloride. Frameshift mutagenesis of the acridines was sequence-specific in that significant activity occurred only with the two strains with a +1 frameshift his C (Salmonella typhimurium strains TA1537 and TA1977) and not with the two strains in which reversion was required at a +2 frameshift in his D (TA1538 and TA1978). Excision repair via uvr B was involved only to a minor extent in the production of a frameshift reversion at the his C locus by the four compounds tested. The dose-response of frameshift reversion at his C induced by the acridine was

nonlinear. These results are consistent with a model derived from nuclear magnetic resonance experiments on 9-aminoacridine binding to dinucleoside phosphates, in which the N-H group is situated in the duplex so as to participate in a hydrogen bond with one base while excluding its complementary partner, thereby provoking mismatching. (18 Refs)

26. BACTERIAL MUTAGENICITY AND TOXICITY OF CYCLOALIPHATIC EPOXIDES.

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Mutat Res; 90(1):67-78 1981

The Ames mutagenicity test with Salmonella was used to investigate mutagenicity of 12 cycloaliphatic epoxides without the addition of liver homogenate fractions. Eight compounds exhibited base-pair substitution mutagenic activity. Mutagenicity decreased with expanding ring size, while inhibition of bacterial growth increased with increasing ring size. Epoxide toxicity at the doses required for mutagenicity prevented establishment of meaningful dose-response relationships. Petri dish sealing bands were used to prevent loss of volatile compounds during 48 hr incubation. Mutagenicity was greater in TA1535 than in TA100; toxicity was more pronounced in TA100. Toxicity was not reduced by the use of less permeable strains (TA92, TA1950, and TA2410). Cyclooctane oxide testing with TA1975 (repair-proficient) and TA1535 (repair-deficient) demonstrated that the bacteria were not being killed by damage to DNA, since toxicity was not reduced in TA1975. The results confirm that cis-1,2-disubstituted oxiranes are mutagenic. (26 Refs)

27. CHROMOSOMAL ANALYSIS IN VINYL CHLORIDE EXPOSED WORKERS: COMPARISON OF THE STANDARD TECHNIQUE WITH THE SISTER-CHROMATID EXCHANGE TECHNIQUE.

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Mutat Res; 83(1):137-144 1981

Twenty-one workers exposed to vinyl chloride (VC) and six controls were subjected to conventional chromosomal analysis (CA) and the determination of sister-chromatid exchanges (SCE). In addition, SCE in human lymphocytes were studied before and after exposure to gaseous VC in vitro. These workers had been subjected to studies 18 mo before. In the exposed workers the av of the different types of abnormalities were significantly increased with CA, while only a slight, nonsignificant, increase of SCE was noted in the exposed group compared with the controls. In lymphocyte cultures exposed to VC during G0/early G1, and late G1/early S phase, no increase in SCE was noted without metabolic activation; a marked decrease was noted with activation and this was independent of cell cycle phase. The small increases of SCE in workers were attributed to low exposures rather than the inability of VC to induce SCE in human lymphocytes; the SCE levels could have returned to normal relatively quickly after exposure. It is suggested that SCE analysis might not be of much value after very low chronic chemical exposures, but might be useful during high chronic chemical exposures and during the first few days after acute exposure. (19 Refs)

28. MUTAGENICITY OF QUINDOXIN, ITS METABOLITES, AND TWO SUBSTITUTED QUINOXALINE-DI-N-OXIDES.

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Antimicrob Agents Chemother; 20(3):336-343 1981

The quinoxaline-di-N-oxides carbadox, olaquindox, and quindoxin, which are potent antibacterial agents, were tested for mutagenicity in the Salmonella microsomal system. They all induced base pair substitutions and frameshift mutations in Salmonella, and occurred independently of the presence of rat liver microsomal fraction in the test system. Mutagenicity was dependent on the presence of their N-oxide groups, since quinoxaline, a completely reduced derivative of quindoxin, was not mutagenic, whereas the partially reduced quinoxaline-N-oxide exhibited a lower mutagenic activity than quindoxin. recA and uvrB Salmonella were found to be more susceptible to mutagenic quinoxaline derivatives than wild-type strains. The mutagenicity of quinoxaline-di-N-oxides was enhanced under anaerobic incubation as was the antibacterial activity. These results suggest that both the antibacterial and mutagenic activity of quinoxalin e-di-N-oxides depend upon the same bacterial activation mechanism. (Author abstract) (26 Refs)

29. MUTAGENICITIES OF CARBADOX AND OLAQUINDOX - GROWTH PROMOTERS FOR PIGS.

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Mutat Res; 90(1):49-55 1981

Both carbadox and olaquindox were positive in the Bacillus subtilis rec and in the Salmonella typhimurium uvr repair tests. In the reverse mutation test with S typhimurium TA100 and TA 98, a linear dose-response relationship was observed for both compounds between 0 and 15 ug/plate. Carbadox was more mutagenic than olaquindox and their activities were marked with strain TA100 (respectively, 315.4 vs 46.3 revertants/ug). In the absence of microsomal supernatant (S9), carbadox was approx 6x more mutagenic than olaquindox; in TA100 with S9, the number of revertant colonies decreased to 146.8/ug with carbadox but only to 38.3/ug with olaquindox. S9 incubation inactivated carbadox almost totally after 10 min, whereas olaquindox retained its activity after 20 min. Carbadox required 20 min to be inactivated by a bacterial cytosol mixture; olaquindox was hardly inactivated after 60 min. Carbadox and olaquindox appear to induce frameshift and base-pair substitution mutations as a result of error in the DNA repair process. Significance of the findings is discussed with respect to use of these compounds as growth promoters in pigs. (18 Refs)

30. DETECTION OF MAMMALIAN CELL MUTAGENS IN URINE FROM CARCINOGEN-DOSED MICE.

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Mutat Res; 90(1):79-90 1981

Urine was collected from male CD-1 mice dosed by oral gavage with either 300 mg/kg 2-aminofluorene (AF), 150 mg/kg cyclophosphamide (CY), or 200 mg/kg lucanthone (LU), and added directly to L5178Y TK+/- mouse lymphoma cultures (heterozygous at the thymidine kinase locus for the induction of trifluorothymidine-resistant (TFT-R) mutants). After 3 hr incubation, urine from the three different groups of rats produced significant, dose-dependent increases in frequency of

TFT-R mutants. When the drugs were tested directly as mutagens in L5178Y TK+/- cells, LU and CY were positive both with and without metabolic activation, but AF required activation. Significant differences in the direct response of Salmonella typhimurium and L5178Y cells to these compounds indicate that the two cell types may not detect the same chemical entities as proximate mutagens. Urinary metabolites of AF, CY, and either the parental molecule or metabolites of LU can readily be detected as mutagens in a mammalian cell assay. (28 Refs)

31. MUTAGENICITY OF CHEMICALS OF INDUSTRIAL AND AGRICULTURAL RELEVANCE IN SALMONELLA , STREPTOMYCES AND ASPERGILLUS.

Principe P, Dogliotti E, Bignami M, Crebelli R, Falcone E, Fabrizi M, Conti G, Comba P
Istituto Superiore di Sanita, Viale Regina Elena 299-00161, Rome, Italy
J Sci Food Agric; 32(8):826-832 1981

Ethylene dibromide (EDB), ethylene dichloride (EDC), propylene dichloride (PDC), allyl alcohol (AA), and sulfallate (S) were tested for their ability to induce reverse mutations (his+ revertants) in Salmonella typhimurium, forward mutations (streptomycin resistance) in Streptomyces coelicolor, and point mutations (8-azaguanine resistance) in Aspergillus nidulans. EDB and S strongly reverted S typhimurium strains TA100 and TA1535;, PDC had a weak effect on these strains; and EDC was weakly active in TA1535 following microsomal activation with rat liver S-9 mix. This mix reduced the mutagenicity of EBD but not that of S. In S coelicolor, EDB was positive only in spot test experiments and S was weakly positive in plate tests; EDC and PDC were inactive in both test systems. In A nidulans, EDB and PCB gave positive responses in the plate and spot tests and S gave a positive response only in the spot test. AA was was not mutagenic in any of the genetic systems. (21 Refs)

32. MUTAGENIC ACTIVITY OF CAFFEINATED AND DECAFFEINATED COFFEE.

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Univ. California, Berkeley, CA, 94720
Cancer Detect Prev; 3(2):507-511 1981

Two types of coffee (caffeinated and decaffeinated) were tested for their mutagenicity using bacterial strains using TA98 and TA100 in Ames Salmonella/Microsome test. According to the Ames criteria, both were found to be mutagenic in the absence of S-9. The mutagens did not require liver enzymes to be activated. (Author abstract) (13 Refs)

33. RELATIONSHIP OF THE RAW WATER QUALITY TO MUTAGENS DETECTABLE BY THE AMES SALMONELLA/MICROSOME ASSAY IN A DRINKING-WATER SUPPLY.

Grabow WO, Van Rossum PG, Grabow NA, Denkhaus R
Natl. Inst. Water Res., Council for Scientific and Industrial Res., P. O. Box 395, Pretoria 0001, South Africa
Water Res; 15(9):1037-1043 1981

The relationship of mutagens detectable by the Ames test to other properties of the Parys, South Africa drinking water supply before and after conventional treatment was studied. The raw water intake was from the Vaal River, subject to pollution with partially purified waste water (nonchlorinated) containing high concentrations of mutagens. Information was obtained on mutagen activity, mutagen formation during conventional water treatment, properties of raw water affecting mutagen concentration in the treated water, and the relation of Ames test results to chemical quality parameters. Mutagens formed during treatment consisted mainly of neutral organic compounds inducing frameshift mutations without liver activation. Although no health hazard was inferred, the results make evident the need for su rveillance of potential carcinogens in conventionally treated water taken from a polluted source. (33 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

34. BINDING OF BENZO(A)PYRENE DERIVATIVES TO SPECIFIC PROTEINS IN NUCLEI OF INTACT HAMSTER EMBRYO CELLS.

MacLeod MC, Kootstra A, Mansfield BK, Slaga TJ, Selkirk JK
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Cancer Res; 41(10):4080-4086 1981

In hamster embryo cells incubated for 24 hr with 4 uM [3H] benzo(a)pyrene, a major portion of the nonextractable radioactivity in nuclear preparations copurifies with the protein fraction. When these proteins are analyzed by sodium dodecyl sulfate:polyacrylamide gel electrophoresis, significant variations in the labeling intensities of the various proteins are seen. Control experiments demonstrate that the labeling is due to covalent binding to protein. Histones H3 and H2A are heavily labeled while the other histones of the nucleosome core, H2B and H4, are devoid of radioactivity. Large amounts of label are associated with proteins with mobilities similar to the very lysine-rich histone H1. However, the results of differential extraction experiments suggest that the labeled proteins do not belong to either the H1 or the high-mobility-group class of chromosomal proteins. During 6 hr of inhibition of protein synthesis by cycloheximide, the metabolism of [3H]benzo(a)pyrene, as monitored by high-pressure liquid chromatography, remained normal. Patterns of labeling of nuclear proteins after 3 or 6 hr were identical in the presence and absence of cycloheximide. This finding strongly suggests that binding of benzo(a)pyrene derivatives to nuclear proteins occurs in situ. (Author abstract) (55 Refs)

35. THE FORMATION AND PERSISTENCE OF BENZO(A)PYRENE METABOLITE-DEOXYRIBONUCLEOSIDE ADDUCTS IN RAT SKIN IN VIVO.

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Int J Cancer; 28(3):387-392 1981

The extent of reaction of benzo(a)pyrene with DNA and the formation of benzo(a)pyrene-deoxyribonucleoside adducts in the skins of male Wistar rats were investigated. Following topical application of benzo(a)pyrene (200 nmoles), binding reached a max of 0.74 pmoles/mg DNA, 12 hr after treatment, and remained high up to 48 hr after treatment. Hydrolysis of the DNA and analysis of the deoxyribonucleoside adducts by HPLC revealed several products. The major adduct, C, (27-40% of the total adducts), co-chromatographed with deoxyribonucleoside adducts formed by reaction of (+-)7beta, 8alpha-dihydroxy-9alpha, 10alpha-epoxy-7,8,9,10-

tetrahydrobenzo(a)pyrene (anti BPDE) with DNA, whilst product B, (19-23% of the total adducts), also formed in significant amounts, co-chromatographed with a further metabolite of 9-hydroxybenzo(a)pyrene bound to an as yet undetermined base in the DNA. Smaller amounts of other deoxyribonucleoside adducts, D and I, were also observed and co-chromatographed with marker compounds derived from reaction of anti BPDE with deoxyadenosine and (+-)7beta, 8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (Syn BPDE) with DNA respectively. There was no evidence for preferential removal of any of the four adducts (B, C, D, and I) during the 48 hr after treatment with benzo(a)pyrene. The relative resistance of rat skin, compared with mouse skin, to benzo(a)pyrene-induced skin carcinogenesis may be due in part to a lower extent of binding of benzo(a)pyrene to DNA, and a smaller percentage of both methanol-soluble hydrocarbon-deoxyribonucleoside adducts and of adducts derived from the putative ultimate carcinogen, BPDE. (Author abstract) (36 Refs)

36. OPTICALLY DETECTED MAGNETIC RESONANCE EVIDENCE FOR CARCINOGEN-NUCLEIC ACID INTERACTION IN THE TETRAHYDRO-9,10-EPOXYBENZO[E]PYRENE-DNA ADDUCT.

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J Am Chem Soc; 103(17):5257-5259 1981

The carcinogenic action of polycyclic aromatic hydrocarbons evidently is mediated by metabolically-activated intermediates which bind covalently to DNA. The optically-detected magnetic resonance technique was used to study the structure of the adduct of tetrahydro-9,10-epoxybenzo[e]pyrene (BePE) with DNA. The pyrene triplet chromophore in the BePE-DNA adduct appears to exist in an environment intermediate between complete intercalation and complete solvent exposure. (21 Refs)

37. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

Bigger CA, Dipple A, Tomaszewski JE, Lake RS
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from those generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

38. DIFFERENCES IN THE BINDING OF 3-METHYLCHOLANTHRENE AND PHENOBARBITAL TO RAT LIVER CYTOSOLIC AND NUCLEAR PROTEIN FRACTIONS.

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Arch Biochem Biophys; 210(2):729-739 1981

In an effort to learn more about the induction of cytochromes P-450c and P-450b, two inducers of these cytochromes, 3-methylcholanthrene (3-MC) and phenobarbital (PB), respectively, were studied in their interactions with proteins from rat serum, rat liver cytosol, and rat liver nuclei. Using DNA-cellulose chromatography, it was demonstrated that 3-MC binds to both cytoplasmic and nuclear components (at approx 27 and 250-570 femtomole/mg of applied protein, respectively) and that PB does not bind to proteins from serum, cytosol, or nuclei that can bind to this chromatographic medium. No binding of PB to cytosolic proteins was demonstrated using DEAE A-50 Sephadex chromatography, charcoal dextran analysis, or sucrose density gradient centrifugation, but the binding of 3-MC to cytosolic proteins gave four peaks of radioactivity by the DEAE technique, two peaks by the sucrose gradient technique, and a specific binding of 0.13 picomole/mg protein by charcoal dextran analysis. One of the sucrose gradient peaks was labile in the presence of 0.3 M KCl, its disappearance being accompanied by an increase in the amplitude of the other peak. Following incubation with whole nuclei, the uptake and intranuclear distribution of 3-MC and PB differed markedly: 64% of the available 3-MC radioactivity but only 3% of the available PB radioactivity became associated with nuclei; moreover, the highest specific activity of this radioactivity was found in different locations, ie, associated with the 2 M KCl-resistant nuclear pellet for 3-MC and with the nuclear fraction soluble in the absence of salt for PB. Nuclear proteins that can bind to both polycyclic hydrocarbons and to DNA have not previously been reported. (43 Refs)

39. METABOLISM OF CHEMICAL CARCINOGENS BY CULTURED HUMAN AND RAT BLADDER EPITHELIAL CELLS.

Autrup H, Grafstrom RC, Christensen B, Kieler J
Lab. Environmental Carcinogenesis, Copenhagen, Denmark
Carcinogenesis; 2(8):763-768 1981

Cells from human bladder epithelium cell lines HU1689, HU1752, and HU1765 and primary bladder epithelial cells from Wistar rats were exposed in vitro for 24 hr to radioactively-labeled carcinogens dissolved in the medium: [1,3,6-3H]benzo[a]pyrene (BP) 1.5 uM; [G3H]aflatoxin B1 (AFB) 1.5 uM; [1 4C]N-nitrosodimethylamine (DMNA) 100 uM; [ethyl-1-14C]N-nitrosoethylmethylamine (EMNA) 100 uM; and [2,5-14C]N-nitrosopyrrolidine (NPy) 100 uM. The metabolism of the carcinogens was assayed by the release of metabolites into the culture medium and the binding of radioactive metabolites to DNA. The human bladder cells retained the capacity to metabolize chemical carcinogens. Binding of DNA occurred to a similar extent in all three cell lines. More BP was bound to DNA in human bladder cells than in rat bladder cells. More than 90% of the metabolites of BP in human cells consisted of organo-soluble products, primarily the 9,10-and 7,8-BP diols. N-nitrosamine metabolism produced CO2. NPy was oxidized in both the alpha and beta positions, predominantly alpha in human cells. EMNA was apparently metabolized, but did not bind to DNA. The results suggest that the human bladder may be able to activate carcinogens that come into direct contact

with the epithelium, and that it utilizes pathways that are different from those found in other tissues and cells. (38 Refs)

40. DNA MODIFICATION IN RAT LUNGS FOLLOWING INTRATRACHEAL OR SUBCUTANEOUS ADMINISTRATION OF 4-NITROQUINOLINE-1-OXIDE, BENZO[A]PYRENE OR 2-AMINOANTHRACENE.

Harpaz R, Mitchell C
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115
Chem Biol Interact; 36(2):129-140 1981

Benzo[a]pyrene (BP)-,2-aminoanthracene (2AA)- and 4-nitroquinoline-1-oxide (4NQO)-mediated DNA modification were investigated in rat lungs by using alkaline sucrose gradient sedimentation. The exposure-route, the physicochemical nature of the administered compound and the number of treatments were all important in determining the extent of DNA modification. 4NQO produced qualitatively similar modification whether instilled intratracheally (it) as a suspension or injected sc in a soluble form. BP and 2AA produced no DNA alteration when injected sc; they did, however, modify DNA sedimentation when instilled as a suspension, but not until 24 hr after treatment. Furthermore, BP caused no DNA modification at any sampling time when instilled in a lipid solvent. In contrast to the DNA modification observed at 24 hr after a single it treatment with a BP suspension, no such alteration was detected 12 or 24 hr after the last of five similar daily treatments. These results are discussed with respect to mechanisms of differential transport, clearance and metabolism of administered carcinogens. (Author abstract) (36 Refs)

41. SPECIFIC LABELLING OF MICROSOMAL PROTEINS BY REACTIVE INTERMEDIATES GENERATED FROM 2-ACETYLAMINOFLUORENE IN VITRO.

Kaderbhai MA, Bradshaw TK, Freedman RB
Biological Lab., Univ. Kent, Canterbury, CT2 7NJ Kent, England
Chem Biol Interact; 36(2):211-227 1981

Incubation of 2-[9-14C]acetylaminofluorene (2-[9-14C]AAF) in vitro with rat live r microsomes, leads to covalent binding of label to microsomal proteins. The binding is NADPH-dependent, increases linearly with time, and is inhibited by SKF-525A and 7,8-benzoflavone (7,8-BF). Binding is increased more than eight-fold in microsomes from 3-methylcholanthrene (MC)-pretreated rats, but only less than two-fold in those from phenobarbital (PB)-pretreated rats. In the presence of cytosolic proteins, there is slight enhancement of the labeling of microsomes and some labeling of the cytosolic proteins. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and two-dimensional gel electrophoresis indicate that covalent labeling by 2-AAF derivatives is concentrated in specific proteins. The pattern of labelling varies between microsomes from animals pretreated with PB, MC and 2-AAF. Factors which may contribute to the specificity of labeling are discussed. (Author abstract) (21 Refs)

42. INDIRECT ALKYLATION OF CBA MOUSE LIVER DNA AND RNA BY HYDRAZINE IN VIVO. A POSSIBLE MECHANISM OF ACTION AS A CARCINOGEN.

Quintero-Ruiz A, Paz-Neri LL, Villa-Trevino S
(c/o Villa-Trevino) Departamento Investigacion, Division de Estudios, Superiores de la Facultad Medicina Universidad Autonoma de Chihuahua, Apart Postal 1506 Sucursal 'C' Chihuahua, Chihuahua, Mexico
JNCI; 67(3):613-618 1981

Treatment of inbred CBA mice with hydrazine sulfate, a liver carcinogen, plus [14C]formate or L-[methyl-14C]-methionine as a source of 'C1' units, produced [14C]7-methyl-guanine (7-MG) in liver DNA and RNA. This methylated guanine was identified by its chromatographic characteristics in three different systems: on Sephadex G10, on Dowex 50, and by paper co-chromatography with authentic 7-MG. Mice that received [14C]formate alone showed no 7-MG in their DNA or RNA. In addition, mice treated with L-[methyl-14C]methionine alone showed no 7-MG in their DNA. These results suggest that 'indirect' alkylation of nucleic acids is a mechanism of cancer initiation by hydrazine. (Author abstract) (20 Refs)

43. ON THE PECULIARITIES OF METHYLATION OF DNA OF DIFFERENT TISSUES OF RAT'S FETUS AND MATERNAL ORGANISM AFTER 1,2-DIMETHYLHYDRAZINE TREATMENT.

Likhachev AYa, Petrov AS
N. N. Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR
Vopr Onkol; 27(7):71-73 1981

A high rate of DNA methylation in the liver and large colon mucosa was registered 6 hr after dimethylhydrazine (SDMH) treatment of rats with 19-day gestations. However, in fetal liver, a low concentration of methylated guanine (7-methyl guanine) derivatives was found, while in large colon and brain, these substances were not detected at all. It is suggested that the resistance of embryonal tissues to the transplacental effect of SDMH is due to the underdeveloped enzymatic system of the fetus. (Author abstract) (8 Refs) (In RUS)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

44. EPOXIDE HYDROLASE ACTIVITY IN THE MITOCHONDRIAL AND SUBMITOCHONDRIAL FRACTIONS OF MOUSE LIVER.

Gill SS, Hammock BD
Dept. Entomology, Univ. California, Davis, CA, 95616
Biochem Pharmacol; 30(15):2111-2120 1981

Distribution of epoxide hydrolase activity in subcellular fractions of livers from male Swiss-Webster mice and Sprague-Dawley rats was monitored with trans-beta-ethylstyrene oxide, trans-stilbene oxide and benzo[a]pyrene 4,5-oxide following differential centrifugation. With the former two substrates the highest activity was encountered in the cytosolic fraction; however, significant activity was found in the mitochondrial fraction. These fractions hydrated benzo[a]pyrene 4,5-oxide very slowly, and the major benzo[a]pyrene 4,5-oxide hydrolyzing activity was recovered in the microsomal fraction. Using Triton WR-1339-treated mice, it was shown that trans-beta-eth-

ylstyrene oxide hydrolyzing activity was predominantly localized in the mitochondria rather than in lysosomes and peroxisomes. Subsequent separation of the mitochondrial fraction into submitochondrial components by swelling, shrinking, and sonication, followed by sucrose density gradient centrifugation, showed that most of the epoxide hydrolyzing activity was present in the matrix and intermembrane space fraction. Significant activity was also present in the outer and inner membrane fractions. However, epoxide hydrolyzing activity in these fractions was reduced if either increased sonication times were used or the fractions were washed, indicating possible contamination of these fractions by the matrix and intermembrane space enzyme(s). The epoxide hydrolase activity in the mitochondrial and cytosolic fractions in mice appeared similar with regard to inhibition, mol wt, and substrate selectivity. (Author abstract) (44 Refs)

45. THE EFFECT OF 3-METHYLCHOLANTHRENE ON URINARY 6BETA-HYDROXYCORTISOL EXCRETION AND HEPATIC ENZYME ACTIVITY IN THE MARMOSET MONKEY (CALLITHRIX JACCHUS).

Challiner M, Park BK, Odum J, Orton TC
(c/o Park) Dept. Pharmacology and Therapeutics, Liverpool Univ., P.O. Box 147, Liverpool L69 3BX, England
Biochem Pharmacol; 30(15):2131-2134 1981

The effect of 3-methylcholanthrene treatment on the urinary excretion of 6beta-hydroxycortisol and hepatic enzyme activity was investigated in the marmoset monkey (Callithrix jacchus). 3-Methylcholanthrene increased cytochrome P-448 content, NADPH cytochrome-c reductase activity, 7-ethoxycoumarin O-deethylase activity and ethoxyresorufin O-deethylase activity but did not affect aminopyrine N-demethylase activity. This induction profile is qualitatively similar to that previously reported for the rat. There was no change in the ratio of urinary 6beta-hydroxycortisol to 17-hydroxycorticosteroids. The pattern of respo nse to 3-methylcholanthrene indicates that cortisol 6beta-hydroxylase activity is not associated with induction of hepatic cytochrome P-488. (Author abstract) (8 Refs)

46. POLYHALOGENATED BIPHENYLS AND PHENOBARBITAL: EVALUATION AS INDUCERS OF DRUG METABOLIZING ENZYMES IN THE SHEEPSHEAD, ARCHOSARGUS PROBATOCEPHALUS.

James MO, Little PJ
Dept. Medicinal Chemistry, Coll. Pharmacy, Univ. Florida, Gainesville, FL, 32610
Chem Biol Interact; 36(2):229-248 1981

Several doses of Aroclor 1254 (polychlorinated biphenyl (PCB) mixture), Firemaster FF1 (polybrominated biphenyl (PBB) mixture), 2,2',4,4',5,5'-hexabromobiphenyl (HBB), 3,3',4,4',5,5'-hexachlorobiphenyl (HCB) and phenobarbital (PB) were administered to the marine fish sheepshead (Archosargus probatocephalus). The PCB and PBB mixtures caused induction of hepatic microsomal benzo[a]pyrene hydroxylase (AHH), 7-ethoxycoumarin O-deethylase (7-EC) and 7-ethoxyresorufin O-deethylase (ERF) activities, but no benzphetamine N-demethylase (BND), epoxide hydrolase (EH), or glutathione S-transferase (GSH-T) activities. This induction pattern is typical of that caused by polycyclic aromatic hydrocarbons (PAH) in fish and mammals or by tetrachlorodibenzo-p-dioxin (TCDD) in mammals. The extent of induction of AHH-activity and cytochrome P-450 content was higher when experiments were carried out in summer (water temperature 25 +-4 C) than in winter (water temperature 11 +-3 C). Firemaster FF1 (15 mg/kg) induced fish for at least 56 days in both summer and winter at which time the liver concentrations of PBB were in the ppm range. PCB concentrations in the ppm range have been found in fish from polluted lakes and seas, thus we may expect that environmental exposure to PCB is sufficient to induce hepatic mixed function oxidase (MFO) activities. The PCB isomer 3,3',4,4',5,5'-HCB, which induces the same spectrum of hepatic drug-metabolizing activities as TCDD and PAH in rats, had a broadly similar effect in the sheepshead. Another purified isomer 2,2',4,4',5,5'-HBB, which induces the same enzymes as PB in rats, had no effect on drug-metabolizing activities in sheepshead. PB was also without effect on sheepshead hepatic drug-metabolizing enzymes, although a typical narcotic effect was produced in PB-treated sheepshead. Our studies provide further evidence that drug-metabolizing activities in fish liver are readily induced by chemicals like TCDD or PAH, but we fail to demonstrate induction after treatment of sheepshead with inducers of the PB type. (Author abstract) (48 Refs)

47. EVIDENCE THAT BENZO(A)PYRENE-RESISTANT, ARYL HYDROCARBON HYDROXYLASE-DEFICIENT VARIANTS OF MOUSE HEPATOMA LINE, HEPA-1, ARE MUTATIONAL IN ORIGIN.

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Lab. Biomedical and Environmental Sciences, Univ. California, Los Angeles, CA, 90024
Somatic Cell Genet; 7(4):373-388 1981

The ability of treatment with known mutagens to increase the frequency of benzo(a)pyrene resistant (BPr) variants was examined. The phenotypic stability of the variants was studied as a function of time in culture and with respect to the degree of heterogeneity among subclones. The in vitro heat lability of the aryl hydrocarbon hydroxylase (AHH) was examined. All strains used were derivatives of the subclone Hepa-1c1c7 of the mouse hepatoma line Hepa-1. Four agents with three distinctly different modes of mutagenic action were used: N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate (alkylating agents), ICR-191G (frame-shift mutagen), and UV light were used. Except for one experiment in which ethyl methanesulfonate only gave a marginal response, the mutagens consistently increased the frequency of BPr clones in a dose-dependent manner. A positive correlation was observed between the frequencies of thioguanine-resistant and BPr clones produced. Many BPr clones possessed considerably reduced, or undetectable AHH activities. Even in those variants that retained considerable AHH activity, heterogeneity in AHH activity among cells of the variants was relatively slight. The sensitivity of BPr variants to the mutagen used for their isolation is described. The in vitro temperature lability of AHH activity in certain BPr variants is discussed. (8 Refs)

48. ALTERATIONS IN DRUG-METABOLIZING ENZYMES DURING FEEDING OF THE CARCINOGEN 2-AMINOANTHRAQUINONE.

Ramanathan R, Reddy TV, Weisburger EK
Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Toxicol Appl Pharmacol; 60(2):204-212 1981

Changes in enzymes which metabolize drugs during periods of feeding with 2-aminoanthraquinone (AAQ), at carcinogenic levels, were studied in young female Fischer 344 rats. Rats were fed 2% AAQ for 2, 4, 8 or 14 wk; after treatment, some were returned to the control diet. Some rats on the control diet were pair-fed with the AAQ group. At least four rats were available for each enzyme determination. Controls were

fed ad libitum. Feeding AAQ increased liver content of cytochrome P-450, cytochrome b5, and increased NADPH-cytochrome c reductase activity as early as 2 wk. After 4 wk of AAQ, there was no change in azodye reductase, although an increase was observed in pair-fed controls. However, after 8 and 14 wk of AAQ, there was a significant increase in dimethylaminoazobenzene reductase. AAQ feeding also led to increased activities of benzo(a)pyrene hydroxylase, epoxide hydrolase, and alpha-naphthol-O-glucuronyl transferase. AAQ feeding beyond 4 wk increased the activities of N-demethylases, aniline hydroxylase and azo reductase. After the experimental period of AAQ feeding, the measured enzyme activities during the recovery period remained elevated in rats fed AAQ for 14 wk for 1 or 2 wk, and 2-4 wk in rats fed AAQ for 8 wk. (22 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

49. EFFECT OF BENZO(A)PYRENE AND ITS NONCARCINOGENIC ANALOG 1,2-BENZOPYRENE ON NA,K-ATPASE ACTIVITY OF HOMOGENATES OF VARIOUS MOUSE ORGANS AND OF MEMBRANE PREPARATION FROM RAT HEART.

Mustafin AM, Kim SCh
Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR
Biull Eksp Biol Med; 91(7):76-77 1981

The effect of benzo(a)pyrene (BP) and its noncarcinogenic analog 1,2-benzopyrene (1,2-BP) on Na, K-ATPase activity was studied in homogenates of albino mice lungs, stomach, and liver. BP caused significant inhibition of enzyme activity in the lungs and in the stomach; the inhibitory effect of 1,2-BP was less pronounced. Both BP and 1,2-BP did not inhibit the enzyme activity of liver homogenate and activity of Na ,K-ATPase from the membranes of rat heart. (5 Refs) (In RUS)

50. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideratio of histological classification of nodules and tumors. Poorly differentiated hepatomas were p
induced by 3'-Me-DAB followed by FAA or D
for hepatomas induced by 3'-Me-DAB followed
bital, which were mainly well and moderately
well and moderately differentiated hepatomas w
nantly induced by FAA followed by 3'-Me-DAB
bital. The degree of enzyme deviation of the
duced by DENA as the first carcinogen was int
tween those of hepatomas induced by FAA or 3'
though the degree tended to increase with incr
term of DENA. These results indicate that devia
enzymes, such as pyruvate kinase and fructose-1,
tase, as well as histological differentiation of the
tomas are more strongly influenc ed by the fir
than by the second under our administration sche
the degree of enzyme deviation shown by hepato
by a particular carcinogen treatment regimen
lates to the potential of that regimen to induce
plastic tumors. (Author abstract) (33 Refs)

51. HEPATOCELLULAR CARCINOMA INDUC ESTROGEN AND PROGESTOGEN: DEVELOP HEPATOCELLULAR CARCINOMA IN RATS FOLLOWING ORAL ADMINISTRATION OF S ESTROGEN AND PROGESTOGEN.

Higashi S
First Dept. Surgery, Mie Univ. Sch. Medicine, Tsu, Ja
Mie Med J; 30(3):295-303 1981

Female Wistar rats were given daily 0.075 mg
tradiol (EES) and 6 mg of norethindrone aceta
solved in olive oil by gavage for 1 yr, another g
similar treatment for 18 mo, and a third group
oil alone for 1 yr and served as controls for the
rats treated with EES and NEA, the liver wt i
kedly, while the body wt decreased. In the rats
mo, the activities of glutamine oxaloacetic tran
tamic pyruvic transaminase, and lactic dehydr
higher and total cholesterol and triglyceride we
those treated for only 1 yr. Multiple nodules ra
mm to 1 mm in diameter were observed in all t
These were hyperplastic nodules with compres
phy of the surrounding liver parenchyma. One o
the first group had a large, 2.5 x 2.0 x 1.5 cm, w
ed hepatocellular carcinoma composed of trab
plastic cells. In rats treated for 18 mo, the nur
plastic nodules was higher and their size was l
mals treated for 12 mo. These results support
that EES and NEA may be initiators in hepato
(30 Refs)

REVIEWS AND OTHER RELEVANT

52. EXPERIMENTAL APPROACHES TOWAR BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin M son, WI, 53706
ACS Symp Ser; 160:197-215 1981

Developments in chemical carcinogenesis r
affect the understanding of malignancy at the

are reviewed. Early observations noted the relationship between exposure of humans to certain substances and the occurrence of certain cancers. This led to laboratory experiments demonstrating the induction of cancers in animals by purified chemicals. Carcinogenesis was further depicted as a two-stage process. The first step involved initiation of cancer potential in cells by a carcinogen. The second step involved promotion of cancer development by a promoting substance that might be different from the initiator. The importance of the presence of various antagonistic carcinogens, enzymes, and metabolites of carcinogens was recognized as affecting the development of cancer or the lack of it. Molecular analysis showed that carcinogens are electrophilic molecules that bind to the DNA molecules in target cells. Current research is exploring the importance of cell cycle phase on carcinogenesis. Cell lineage and genotypic cell markers are being studied as tools for cancer research. (91 Refs)

53. APPLICATION OF A GEOMETRIC PARAMETER DEFINING MOLECULAR SHAPE, FOR THE QUANTITATION OF INTERACTION OF POLYCYCLIC AROMATIC HYDROCARBONS WITH ENZYME SYSTEMS.

Lamparczyk H, Radecki A, Kaliszan R
Faculty Pharmacy, Medical Academy, K. Marksa 107, 80-416 Gdansk, Poland
Biochem Pharmacol; 30(16):2337-2341 1981

Quantitative relationships between the ability of polycyclic aromatic hydrocarbons to induce and repress various enzyme systems and a geometric parameter expressing their molecular shape have been described. In contrast, no statistically significant relationship was found when quantum-chemical parameters characterizing the reactivity and donor-acceptor properties of these compounds were correlated with their biological activity. (Author abstract) (17 Refs)

54. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

55. UPTAKE OF LIPOPHILIC CARCINOGENS BY PLASMA LIPOPROTEINS. STRUCTURE-ACTIVITY STUDIES.

Shu HP, Nichols AV
Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720
Biochim Biophys Acta; 665(3):376-384 1981

This report describes the interaction between plasma lipoproteins and two hydroxylated metabolites of benzo[a]pyrene, 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-7,8-dihydrodiol, whic h differ significantly in lipophilicity. When incubated with plasma, the metabolites of benzo[a]pyrene exhibit a decreasing distribution into the ultracentrifugal lipoprotein fraction (d less than or equal to 1.20) and an increasing distribution into the albumin-rich fraction (d greater than 1.20) as the degree of hydroxylation of the metabolite increases. At saturation, uptake of benzo[a]pyrene by VLDL, LDL and HDL correlates with lipoprotein total-lipid vol. Uptake of hydroxylated derivatives per lipoprotein total-lipid vol, in general, decreases with increasing hydroxylation. Contrary to this trend, HDL uptake of 3-hydroxybenzo[a]pyrene at saturation is significantly higher than its uptake of benzo[a]pyrene. Uptake of benzo[a]pyrene-7,8-dihydrodiol per total-lipid vol by all of the lipoprotein classes at saturation is considerably lower than their uptake of 3-hydroxybenzo[a]pyrene. Factors in addition to lipid solubility substantially alter lipoprotein uptake of the metabolites. (Author abstract) (15 Refs)

56. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr(VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the

cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

57. THE ROLE OF GENETIC TOXICOLOGY IN A SCHEME OF SYSTEMATIC CARCINOGEN TESTING.

Williams GM, Weisburger JH, Brusick D
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:57-87 1981

No single test has been developed for detecting all hazardous chemicals. It is therefore important to formulate the criteria for selecting the best combination of tests for a test battery. A battery should combine detection and confirmation of a hazard in one step. It should be capable of including all types of hazards. The tests should have clear biological significance and should maximize metabolic parameters. The Decision Point Approach involves five sequential steps in evaluating the carcinogenic potential of a chemical. First the structure of the chemical is determined. Then a series of in vitro short-term tests are run. These tests include bacterial mutagenesis, DNA repair, mammalian mutagenesis, sister chromatid exchange, and cell transformation. The evidence provided by the tests is evaluated. A suspected chemical is tested in limited in vivo assays for skin tumor induction in mice, pulmonary tumor induction in mice, breast cancer induction in female Sprague-Dawley rats, and altered foci induction in rodent liver. Further evaluation is made. Chronic bioassays complete the series of tests. A final evaluation of all the tests is made, allowing a decision to be made on the hazard of the chemical in question. (63 Refs)

58. PANCREATIC CANCER.

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Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

The objectives of the International Union Against Cancer Workshop were to bring together a small group of active workers in the basic aspects of pancreatic cancer (PC) with the hope that by their carefully planned interchange, they might summarize current information and provide some guidelines for future research. Topics discussed included the epidemiology of PC (international incidence data, time trends, urban/rural differences, socioeconomic differences, and risk factors), pathology of PC (nonendocrine: types of PC), cell structure and function of endocrine PC (synopsis of current views on pancreatic islet cytology, analysis of cell structure and secretory products in endocrine PCs, experimental tumors, mixed endocrine-exocrine PC, and perspectives for future work), carcinogenesis (pancreatic carcinogenesis, carcinogen metabolism, and histogenesis of PC), animal models, biology of pancreatic tumor cells, tumor markers (carcinoembryonic antigen (CEA), pancreatic oncofetal antigens (POA), comparison of POA and CEA, search for other new PC markers, comparison of CEA and anti-CEA reactive substances in colonic and pancreatic tumors, identification and evaluation of protein degradation products resulting from protease activities associated with PC, leukocyte adherence inhibition, galactosyl transferase isoenzyme in PC, and radioimmunodetection), effects of diet on the exocrine pancreas, aims and decision in PC with regard to the relationship between tumor and host (current methods of treatment, prognostic factors, and therapeutic strategy), and conclusions and recommendations for future work. (432 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernizola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.
Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.
Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.
Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.
Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.
Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.
Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.
Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.
Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.
Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).
Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
In RUS

15. LIFESTYLE AND CANCER.
Higginson J
International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.
Zamfir G, Diaconu R
Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.
Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.
Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

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International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.
Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.
Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
In RUS

23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.
Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

24. BURKITT'S LYMPHOMA.
Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.
Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.
Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Test: (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.
Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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ICRDB CANCERGRAM

MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/02 FEBRUARY, 1982

This Cancergram is a service of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM of the U.S. National Cancer Institute. Every few weeks, an updated Cancergram containing abstracts of selected cancer-related articles recently published in more than 3000 journals, and dealing with the topic indicated by the above title, is sent to researchers working in this area. These researchers are identified on the basis of the description of their current research project that has been submitted to the ICRDB Program, directly or via granting agencies.

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METABOLIC ACTIVATION OF CARCINOGENS

1. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

Elucidation of the structures of active polycyclic aromatic hydrocarbon metabolites and of the pathways leading to their formation are reviewed with respect to implications for the mechanism of cancer induction. Major topics discussed include

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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metabolism, K-region arene oxides, diol epoxide metabolites of other polyarenes, diol epoxide-nucleic acid interaction, and theories of carcinogenesis. Although much is now known in the areas of metabolic activation and tumor initiation, unanswered questions remain concerning the relation of DNA alkylation and tumor induction, regioselectivity of alkylation, fidelity of transcription, and nucleic acid repair and errors during repair. (123 Refs)

2. ENZYMATIC METHYLATION OF MICROSOMAL METABOLITES OF BENZO(A)PYRENE.

Lombardi PE, Mayhew JW, Goldin BR, Gregory ME, Lynch MA, Sullivan CE, Gorbach SL
(c/o Mayhew) Infectious Disease Service, New England Medical Center Hosp., 171 Harrison Ave., Boston, MA, 02111
Cancer Res; 41(11,part1):4415-4419 1981

These studies suggest that the microsomal metabolism of benzo(a)pyrene (BP) produces metabolites which can be methylated by the catechol-o-methyltransferase (COMT)/S-adenosylmethionine (SAM) enzyme/donor combination. Induced microsomes converted 12 to 15% of substrate BP to polar products. Approx 0.06% of substrate BP was recovered as COMT/SAM-reactive substances. In tests for specificity, COMT/SAM was found to react with catechols, but not with dihydrodiols, quinones, a phenol, an epoxide, or 1,4-hydroquinone. Organic extracts of COMT/[14C]SAM incubations with BP were fractionated by high-performance liquid chromatography. The appearance of radiolabeled chromatographic bands required the presence of substrate BP, microsomes, and COMT/[14C]SAM. When the Ames mutagenesis assay was supplemented with COMT/SAM, a 36% reduction was observed in the number of revertant colonies induced by the microsomal oxidation of BP. In contrast, the mutagenic properties of 2-aminofluorene were not affected by COMT/SAM. These observations indicate that COMT/SAM does not generally inhibit mixed-function oxidase activity but rather reacts with substances which are activated by ring oxygenations. (Author abstract) (33 Refs)

3. REDUCTION OF TUMORIGENICITY AND OF DIHYDRODIOL FORMATION BY FLUORINE SUBSTITUTION IN THE ANGULAR RINGS OF DIBENZO(A,I)PYRENE.

Hecht SS, LaVoie EJ, Bedenko V, Pingaro L, Katayama S, Hoffman D, Sardella DJ, Boger E, Lehr RE
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Res; 41(11,part1):4341-4345 1981

The tumor-initiating activities on mouse skin and in vitro metabolism of dibenzo(a,i)pyrene, 2-fluorodibenzo(a,i)pyrene, 3-fluorodibenzo(a,i)pyrene, and 2,10-difluorodibenzo(a,i)pyrene were compared. After an initiating dose of 500 ug, followed by promotion with tetradecanoylphorbol acetate, dibenzo(a,i)pyrene induced skin tumors in 85% of the mice and caused 5.8 skin tumors/mouse. The corresponding tumorigenic activities for the fluorinated compounds were: 2-fluorodibenzo(a,i)pyrene (85%; 1.7 tumors/mouse); 3-fluorodibenzo(a,i)pyrene (80%; 3.1 tumors/mouse); and 2,10-difluorodibenzo(a,i)pyrene (10%; 0.1 tumors/mouse). After an initiating dose of 100 ug, only dibenzo(a,i)pyrene s howed significant tumor-initiating activity. 3,4-Dihydro-3,4-dihydroxydibenzo(a,i)pyrene was identified as a metabolite of dibenzo(a,i)pyrene formed by the 9000 x g supernatant from the livers of Aroclor 1254-pretreated rats. Another dihydrodiol was tentatively identified as 1,2-dihydro-1,2-dihydroxydibenzo(a,i)pyrene. The formation on these angular ring dihydrodiols was inhibited in the metabolism of 2-fluorodibenzo(a,i)pyrene and 3-fluorodibenzo(a,i)pyrene. Angular ring dihydrodiols were not detected in the metabolism of 2,10-difluorodibenzo(a,i)pyrene. These results suggest that an angular ring dihydrodiol, 3,4-dihydro-3,4-dihydroxydibenzo(a,i)pyrene, which can form a bay-region dihydrodiol epoxide, may be a proximate carcinogen of dibenzo(a,i)pyrene. (Author abstract) (25 Refs)

4. QUANTUM CHEMICAL STUDIES OF METHYL AND FLUORO ANALOGS OF CHRYSENE: METABOLIC ACTIVATION AND CORRELATION WITH CARCINOGENIC ACTIVITY.

Poulsen MT, Loew GH
(c/o Loew) Life Sciences Div., SRI International, 333 Ravenswood Ave., Menlo Park, CA, 94025
Cancer Biochem Biophys; 5(2):81-90 1981

Specific electronic properties related to metabolic transformation and adduct formation by DNA were calculated for a series of methyl, dimethyl and n-fluoro-5-methyl derivatives of chrysene with the aim of identifying molecular properties which could be used as reliable indicators of their relative carcinogenic behavior. Using the semiempirical all valence electron IEHT method, the bay region bonds of 5MC were found to have enhanced nucleophilic reactivity to epoxide formation relative to chrysene. In addition, in one of the nonequivalent bay regions, the 1, 2, 3, 4 region, the distal (1, 2) bond was found to be more reactive than the proximal (3, 4) bond. This reactivity pattern leads to an easily formed diol epoxide carbocation, the postulated ultimate carcinogen. By contrast, in the other (7, 8, 9, 10) bay region, the proximal (9, 10) bond is the more reactive, suggesting formation of the 'wrong,' ie, less stable diol epoxide carbocation. Consistent with earlier studies of other PAH, calculations by the INDO method of the ease of carbocation formation from a bay region diol epoxide yielded a set of values which gave a good correlation with carcinogenicity. (Author abstract) (29 Refs)

5. STUDIES IN THE METABOLISM OF CARCINOGENIC POLYCYCLIC HETEROAROMATIC COMPOUNDS. I. THE HEPATIC MICROSOMAL METABOLISM OF 7-METHYLBENZ[C]ACRIDINE.

Ireland CM, Holder GM, Ryan AJ
(c/o Holder) Dept. Pharmacy, Univ. Sydney, New South Wales 2006, Australia
Biochem Pharmacol; 30(19):2685-2690 1981

An enzyme assay for the metabolism of the carcinogenic aza-aromatic polycyclic compound 7-methylbenz[c]acridine has been developed using a modification of a radiochemical assay described for the polycyclic aromatic hydrocarbon benzo[a]pyrene by DePierre et al and Van Cantfor t et al. When the activities of controlled microsomes and microsomes of phenobarbital-, 3-methylcholanthrene- and 7-methylbenz[c]acridine-pretreated animals were compared, strong similarities were displayed toward oxidation of benzo[a]pyrene and 7-methylbenz[c]acridine. These similarities were seen in turnover numbers, Michaelis constants, and inducibility of both enzyme systems. 7-Methylbenz[c]acridine afforded a Type I difference spectrum with 3-methylcholanthrene-pretreated microsomes. It is suggested that 7-methylbenz[c]acridine is oxidized by the same or a similar set of enzymes which is responsible for benzo[a]pyrene metabolism. (Author abstract) (39 Refs)

6. RELATIONSHIP OF METABOLIC ACTIVATION OF N-HYDROXY-N-ACYLARYLAMINES TO BIOLOGICAL RESPONSE IN THE LIVER AND MAMMARY GLAND OF THE FEMALE CD RAT.

Shirai T, Fysh JM, Lee M, Vaught JB, King CM
(c/o King) Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4346-4353 1981

Ip injection of the N-formyl, N-acetyl, or N-propionyl derivatives of N-hydroxy-4-aminobiphenyl, N-hydroxy-2-acetylaminofluorene, or N-(4-biphenyl)glycolamide disclosed that the ability of these compounds to induce mammary tumors in the female CD rat was greater if the compound was able to be metabolized to a reactive product by one of two solubie enzymes obtained from both the liver and mammary gland. A similar but weaker association between the formation of gamma-glutamyltranspeptidase-positive foci and cellular altered foci of the liver was also observed. The enzyme related to the tumorigenicity of these compounds was characterized by a highly specific capacity to form adducts from the acetyl and propionyl derivatives. The other enzyme exhibited greater activity with N-formyl substrates. The two enzyme activities were separable by ion-exchange chromatography on DEAE-cellulose and by gel filtration of Sephacryl. Liver microsomes also possessed the capacity to activate both the formyl and acetyl derivatives to reactive species; formyl substrates were 7 to 8x more active than acetylated compounds. The microsomal activities and the formyl-preferring soluble enzyme were inhibited by diethyl-p-nitrophenylphosphate, a microsomal deacylase inhibitor. The cytosolic enzymes that are most active with the acetyl and propionyl substrates were little affected by this organophosphate compound. The microsomal activation was not due solely to deacylation of the hydroxamic acids, since formylated and acetylated substrates were hydrolyzed at approx the same rates. (Author abstract) (37 Refs)

OTHER METABOLISM OF CARCINOGENS

7. DIFFERENCES IN ROUTES OF CONJUGATION WITH GLUCURONIC ACID AND SULPHATE IN NORMAL AND CANCEROUS TISSUE FROM HUMAN LUNG.

Mehta R, Gibby EM, Cohen GM
Div. Toxicology, Dept. Biochemistry, Univ. Surrey, Guildford GU2 5XH, Surrey, En gland
Biochem Soc Trans; 9(1):110-111 1981

Lung tumor tissue from five patients and normal peripheral lung tissue from the same patients was treated in culture with 20 uM labeled 1-naphthol. After incubation, culture medium was analyzed for glucuronide and sulfate conjugates by thin layer chromatography. Radioactivity retained in the medium accounted for 70-90% of the original amount added. Unmetabolized 1-naphthol in the medium varied from 37.7-91.9% for normal lung tissue and from 55.9-99.0% for tumor tissue. The primary metabolite formed by normal tissue was 1-naphthyl sulfate (1-NS: 6.4-59.9%), with no detectable 1-naphthyl glucuronide (1-NG). The primary metabolite formed by tumor tissue was 1-NG (0.3-39.8%), with little or no 1-NS (0.7-1.0%). Tumor tissue from one patient formed no detectable conjugates of either type. Evidently tumorigenesis is accompanied by the appearance of a conjugation system that has little or no activity in normal host lung tissue. This may have significance in the exploitation of biochemical differences between normal and tumor tissues for production of selective chemotherapeutic effects on cancer cells. (5 Refs)

8. GLUCURONIC ACID AND SULPHATE ESTER CONJUGATION IN HUMAN LUNG CANCER CELL LINES.

Gibby EM, Mehta R, Ellison M, Cohen GM
Div. Toxicology, Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Biochem Soc Trans; 9(1):111 1981

Eight cell lines derived from human lung tumor tissue were incubated with radioactively-labeled 1-naphthol (1-N: 10 uM) or hydroxybenzo[a]pyrene (HBP: 2 uM) for 90 min. Conjugates of 1-N and HBP in the culture medium were analyzed by thin-layer chromatography. Generally 1-N was metabolized to a greater extent than HBP. Four of the cell lines formed the glucuronide conjugate (GC) of 1-N. Two of these cell lines formed GC extensively and exclusively. Three cell lines did not metabolize 1-N. One produced only the sulfate conjugate (SC). The GRi and Ben cell lines, derived from poorly-differentiated epidermoid carcinomas, produced more GC [3.93 and 16.65 nanomoles/mg protein/90 min (nm/mg/t), respectively] than SC (less than 0.01 nm/mg/t for both lines). Results with HBP were similar for the two lines, but at lower rates (0.03 and 0.20 nm/mg/t, respectively). E14, derived from squamous cell carcinoma, and Poc and Mar, derived from oat-cell tumors, produced little or no conjugate of either type. Min, derived from adenocarcinoma, produced more GC (6.31 nm/mg/t) than SC (1.07 nm/mg/t). Mor, derived from anaplastic tumor, produced more GC (2.89 nm/mg/t) than SC (1.19 nm/mg/t). Dre, also from anaplastic tumor, produced more SC (0.95 nm/mg/t) than GC (0.01 nm/mg/t). Lack of SC production in some lines may be due to absence of sulfotransferase or inability to form a sulfate donor. Evidently different cell lines follow different patterns of conjugation. (2 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

9. BIOCHEMICAL MECHANISM OF MODULATION OF SKIN CARCINOGENESIS BY RETINOIDS.

Verma AK
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Investigations of mechanisms involving retinoids in the two-stage model of mouse skin carcinogenesis are reviewed. Application of retinoic acid (RA) 1 hr before application of 12-O-tetradecanoylphorbol-13-acetate (TPA) led to inhibition of induction of ornithine decarboxylase (ODC) and resultant putrescine accumulation, and inhibition of enhanced DNA synthesis at 18 hr, but not at 24 or 48 hr. RA did not inhibit S-adenosylmethionine decarboxylase induction, incorporation of [3H]leucine or [3H]histidine into epidermal protein, induction of cyclic AMP phosphodiesterase activity, accumulation of prostaglandins E and F, or hyperplasia occurring 1 or 3 days after TPA treatment. No increase in polyamine biosynthesis was detected after topical skin treatment with 17 nanomole RA, but incorporation of [3H]thymidine increased at 42 hr. RA inhibited skin papillomas and carcinomas when administered with TPA treatments, but not when given with initiating doses of 7,12-dimethylbenz[a]anthracene (DMBA) after repeated

TPA doses. RA did not promote growth of DMBA-induced tumors. Combined RA and DMBA treatment did not result in inhibition of induction of ODC or tumors. (58 Refs)

10. BIOLOGICAL EFFECTS OF RETINOIDS.

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Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The final paper presents a summary and conclusions of the meeting. Comments are presented on many subjects including transport, metabolism, side effects, teratogenicity, mutagenicity, effect on epithelial proliferation, differentiation, tumor growth, immunity and antiinflammatory effects of retinoids. (no Refs)

11. BETA-NAPHTHYLISOTHIOCYANATE-INDUCED ALTERATIONS IN HEPATIC DRUG METABOLISM AND LIVER MORPHOLOGY.

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Toxicol Appl Pharmacol; 60(3):527-534 1981

The effects of continuous feeding with beta-naphthylisothiocyanate (BNIT: 0.022%, 0.047%, or 0.1% of diet for 4 wk) on liver histology and hepatic enzymes were studied in male Charles River F-344 rats. Rats fed 0.1% BNIT developed multifocal granulomatous inflammatory lesions, but the lesions did not alter SGPT or serum bilirubin levels. BNIT treatment resulted in a dose-dependent increase in hepatic cytochrome P-450, benzphetamine-N-demethylase, and ethoxycoumarin-O-deethylase activity. BNIT also stimulated DT-diaphorase activity, but it did not alter epoxide hydrolase activity assayed with benzo(a)pyrene-4,5-oxide or styrene oxide as substrates. These effects contrast markedly with those of alpha-naphtylisotiocyanate. which also inhibits chemically induced hepatocarcinogenesis. Stimulation of mixed-function oxidases and DT-diaphorase may be a factor in the anticarcinogenic action of BNIT. (36 Refs)

12. EFFECTS OF PHENOBARBITAL PRETREATMENT ON THE METABOLISM AND TOXICOKINETICS OF AFLATOXIN B1 IN THE RHESUS MONKEY.

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Toxicol Appl Pharmacol; 60(3):387-397 1981

Five male rhesus monkeys were treated with phenobarbital (PB: 15 mg/kg, 2 x/day) for 1 wk prior to administration of aflatoxin B1 (AFB1: 0.1-1.0 mg/kg, iv). PB pretreatment enhanced the in vitro conversion of AFB1 to aflatoxin Q1 and aqueous metabolites in monkey liver. Although PB did not appreciably alter the rate or vol of AFB1 distribution in vivo, it reduced plasma levels of total aflatoxins, AFB1, and the toxic metabolite aflatoxin M1 (AFM1). Decreased AFM1 levels and increased levels of less toxic water-soluble metabolites were found in the urine of PB-treated monkeys. These findings demonstrated that increased hepatic AFB1 metabolism results in elimination and circulation os less toxic, less mutagenic, and highly excretable metabolites. (49 Refs)

13. EFFECT OF PHENOBARBITAL PRETREATMENT ON THE TOXICITY AND METABOLISM OF 2,4-DIAMINOANISOLE.

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Biochem Pharmacol; 30(19):2715-2718 1981

The effects of phenobarbital (PB) on the acute toxicity, macromolecular binding, disposition, and metabolism of 2,4-diaminoanisole (2,4-DAA) were studied in young male Fischer rats. At 5 and 24 hr after ip injection of [14C]-2,4-DAA, the highest concentration in control and PB-pretreated animals occurred in the kidney. Lower levels were found in the liver, spleen, lung, heart, and testis, respectively. The higest concentration of 2,4-DAA bound to tissue macromolecules was found in the kidney, followed by the liver, spleen, lung, heart, and testis, respectively. Concentrations of bound materials at 24 hr were approx half of those observed at 5 hr. Pretreatment with PB significantly increased binding, but only in the liver and kidney and not in other organs. In control rats, who received equal vol of NaCl and [14C]-2,4-DAA, 31% of the 14C dose was found in the urine in 5 hr, and 69% by 24 hr. In PB-pretreated rats, the rate of excretion of radioactivity was somewhat faster than that of the control animals: 42% of the radioactivity was in the urine at 5 hr. No difference in the excretion of total radioactivity or of the radioactivity in each fraction was observed between the PB-pretreated and control groups at the 24 hr period. The high pressure liquid chromatography separation of the five known metabolites of 2,4-DAA in control and PB-pretreated rats is described. The acute toxicity of 2,4-DAA was increased by PB treatment as evidenced by a change in the LD50 dose from 116 mg/kg to 97 mg/kg in the PB-pretreated rats. The mechanism and implications of the PB-related effects on 2,4-DAA metabolism are discussed. (14 Refs)

14. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

15. INFLUENCE OF MICROSOMAL AND CYTOSOLIC FRACTIONS FROM RAT, MOUSE, AND HAMSTER LIVER ON THE MUTAGENICITY OF DIMETHYLNITROSAMINE IN THE SALMONELLA PLATE INCORPORATION ASSAY.

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Cancer Res; 41(11,part1):4361-4367 1981

Dimethylnitrosamine (DMN) was mutagenic in the Salmonella plate incorporation assay (Ames test) at a level of 10 umol/plate (3.7 mM) in the presence of hamster liver S-9. Mutagenicity of DMN at this level was not observed when the S-9 was derived from mouse or rat liver, although the mouse liver and hamster liver S-9 had similar DMN demethylase activities. Both mouse and rat liver S-9 inhibited the mutagenicity of DMN mediated by hamster liver S-9; the inhibitory factor was contained in the microsomal fraction. Mouse or rat liver microsomes did not inhibit the DMN demethylase activity of hamster liver S-9. The microsomal inhibitor from rat or mouse liver was stable at 60 but was inactivated at 70 C. DMN demethylase from both rat and mouse liver was inactivated at 60 C. Although the DMN demethylase activity of hamster liver S-9 was contained in the microsomal fraction, DMN mutagenesis under conditions of the assay required the presence of both microsomal and cytosolic (S-105) fractions; the cytosols from hamsters, mice, and rats were all effective. The cytosolic factor required for DMN mutagenesis was sensitive to trypsin and was not dialyzable. The presence of an inhibitor of DMN activation in rat and mouse microsomes may account for, or contribute to, the failure of liver S-9 preparations from these species to activate DMN to a mutagen under standard conditions of the Ames test. The requirement for the cytosolic fraction may indicate that DMN demethylase is not sufficient for the activation of DMN to a mutagen under the conditions used in these studies. (Author abstract) (46 Refs)

16. GREATER EFFECTIVENESS OF HEPATOCYTE AND LIVER S9 PREPARATIONS FROM HAMSTERS THAN RAT PREPARATIONS IN ACTIVATING N-NITROSO COMPOUNDS TO METABOLITES MUTAGENIC TO SALMONELLA.

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Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
JNCI; 67(5):1117-1122 1981

A comparison was made of the ability of liver S9 and hepatocyte preparations from noninbred Syrian golden hamsters and noninbred Sprague-Dawley rats to metabolically activate a number of nitroso compounds in the Salmonella mutagenesis assay. The liver S9 and hepatocyte preparations from hamsters were consistently more effective than were preparations from rats in metabolizing nitrosodimethylamine (NDM), nitrosodiethylamine, nitrosodiallylamine, nitrosopyrrolidine (NP), nitrosomorpholine (NM), nitrosodiethylmethylurea (NDEMU), and nitrosodimethylethylurea (NDMEU) to mutagenic forms. The use of hamster S9 preparations with NP and NM resulted in up to 14x the number of revertant colonies obtained with rat preparations; in the presence of hamster hepatocytes, up to 32x the number of revertants were obtained. The S9 preparations from male hamsters not treated with the enzyme inducers phenobarbital and Aroclor 1254 were more effective than were those from female hamsters for activating NP, NM, and NDM. NDEMU and NDMEU, which have been reported to be carcinogens but not mutagens, were mutagenic in the presence of induced liver S9 or hepatocyte preparations from hamsters but not from rats. When tested with any of the S9 or hepatocyte preparations, nitrosodiphenylamine and nitrosomethylaniline, also reported to be carcinogens but not mutagens, gave no mutagenic responses. Nitrosodioctylamine, which has been reported to be noncarcinogenic, was also not mutagenic. (Author abstract) (23 Refs)

17. ENHANCEMENT OF N-HYDROXY-2-AMINOFLUORENE BACTERIAL MUTAGENICITY BY THE SOLUBLE PROTEIN FRACTION FROM RAT LIVER AND PARTIAL PURIFICATION OF THE ENHANCEMENT ACTIVITY.

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Cancer Res; 41(11,part1):4600-4605 1981

Bacterial mutagenesis from 2-aminofluorene mediated by washed rat liver microsomes was elevated 2-to 3-fold by addition of the hepatic soluble protein fraction. Enhancement was observed at 2-aminofluorene concentrations between 1 and 20 ug/assay but not at 30 to 50 ug/assay. The soluble protein fraction (without added microsomes) did not activate 2-aminofluorene for bacterial mutagenesis. However, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was enhanced by the soluble protein fraction, but only when reduced nicotinamide adenine dinucleotide phosphate was also present. On the basis of chemical assay, reduced nicotinamide adenine dinucleotide phosphate reduced 2-nitrosofluorene to N-hydroxy-2-aminofluorene and protected the hydroxylamine from oxidation, thus indicating that it was the mutagenicity of N-hydroxy-2-aminofluorene (but not 2-nitrosofluorene) which was enhanced by the soluble protein fraction. Without the added soluble protein fraction, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was unaffected by reduced nicotinamide adenine dinucleotide phosphate. We succeeded in partially purifying a protein fraction with properties of the enhancement activity. The partially purified fraction, which represents a 14-fold increase in specific activity, was assigned a mol wt of 33,500 by gel filtration through Sephadex G-100. This fraction was resolved into three components by polyacrylamide gel electrophoresis; the mol wt of the three components were determined by sodium dodecyl sulfate-polyacrylamide gel (10%) electrophoresis to be 33,000, 27,000, and 16,250. The mechanism of mutagenesis enhancement remains unknown. (Author abstract) (27 Refs)

18. MUTAGENICITY OF ISOMERIC BETA, GAMMA, GAMMA-UNSATURATED N-NITROSAMINES DERIVED FROM TERPENE ALKANOLAMINES.

Abidi SL, Finch RA
P. O. Box 65, La Crosse, WI, 54601
Environ Mutagen; 3(5):587-591 1981

The Ames Salmonella/microsome mutagenicity test was performed on a 1:2 mixture of cis-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (cis-NDOA) and trans-N-nitroso-2(3',7'-dimethyl-2',6' octadienyl)aminoethanol (trans-NDOA). With the cis,trans-NDOA mixture, tested at dose levels of 50, 100, and 250 ug/incubation mixture (IM), without S-9 activation, no significant increase in the number of revertant colo-

nies/plate was seen in any of the tester strains and no dose-response relationship was noted. At doses of 50o and 100 ug/IM in the presence of S-9 activation, significantly greater numbers of revertant colonies were noted only in tester strains TA100 and TA1535. A cytotoxic effect was noted in all the tester strains at a dose level of 250 ug/IM. A slight cytotoxic effect was noted in strain TA1535 at a dose level of 100 ug/IM. it was concluded that under the conditions of the test, the mixture of cis and trans isomers of NDOA is mutagenic for the Salmonella tester strains TA100 and TA1535 in the presence of Aroclor 1254-induced rat liver S-9 activation system. (6 Refs)

19. INDUCTION OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CULTURED MAMMALIAN CELLS BY N-NITROSOCIMETIDINE.

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Cancer Lett; 14(1):71-75 1981

The possibility that N-nitrosocimetidine (NC), formed by the nitrosation of cimetidine (used in the treatment of gastric disorders), induces sister chromatid exchanges (SCE) and chromosomal aberrations in cultured Chinese hamster ovary cells (CHO) was investigated. NC caused a concentration-related increase in both SCE and chromosome aberrations in a concentration as low as 1.2 x 10(-7) M. At a concentration of 1.2 x 10(-4) M the number of SCE was too great to allow accurate counting and chromosome aberrations were induced in more than 90% of the metaphases. The chromosome aberrations observed were all of the chromatid type. On a molar basis, NC was approx two-thirds as potent an inducer of SCE as the gastric carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. These findings constitute further evidence that NC possesses carcinogenic activity. (10 Refs)

20. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs. The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, r eduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

21. SPECIES DIFFERENCE IN N-HYDROXYLATION OF A TRYPTOPHAN PYROLYSIS PRODUCT IN RELATION TO MUTAGENIC ACTIVATION.

Yamazoe Y, Kamataki T, Kato R
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Cancer Res; 41(11,part1):4518-4522 1981

Metabolic activation of a tryptophan pyrolysate, 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), in liver microsomes from rats, mice, hamsters, guinea pigs, and rabbits was studied to know whether N-hydroxylation is a common obligatory step for mutagenic activation of Trp-P-2. Among hepatic microsomes obtained from untreated animals, the highest activity of Trp-P-2 N-hydroxylase was observed in microsomes from hamsters, followed by those from guinea pigs, mice, and rabbits. In rats, the activity was low, and there was no appreciable difference between the sexes. The activity of Trp-P-2 N-hydroxylase in microsomes was increased by pretreating the animals with a polychlorinated biphenyl mixture. The induction was most profound in rats, and the activity was enhanced 257-fold, as compared to that of untreated animals. The activity was also enhanced in microsomes from polychlorinated biphenyl mixture-treated rabbits, mice, and hamsters, while the activity was increased only slightly in guinea pigs and was thereby lowest among microsomes from the polychlorinated biphenyl mixture-treated animals. In bacterial mutagenesis test systems using Salmonella typhimurium TA 98, the number of revertants induced by Trp-P-2 was increased in parallel with the microsomal ability of the N-hydroxylation. These results indicate that in all species examined N-hydroxylation is an essential metabolic step for mutagenic activation of Trp-P-2. (Author abstract) (32 Refs)

22. THE MUTAGENIC EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM II AND ITS DEGRADATION PRODUCTS IN THE AMES MICROBIAL ASSAY.

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Environ Mutagen; 3(5):555-563 1981

The Ames microbial mutagenicity assay was used to test the mutagenicity of cis-diamminedichloroplatinum (II) (cis-DDP) and its degradation products (obtained from a soln aged for 12 mo at 37 C), platin B salt, magnus red, and magnus red anion salt in order to determine if the positive mutagenic response of the platinum compound could be due to, or enhanced by, the presence of degradation products. A significant increase in hist+-revertants occurred with Salmonella strains TA98, TA100, TA92, and TA94 with platin B salt, magnus red, magnus red anion salt, and lyophilized cis-DDP. The aged cisplatin, however, exhibited an increase only with strains TA100, TA92, and TA94. All degradation products exhibited a slight but significant mutagenic effect with strains TA1535 and TA1537. The mixed function oxidase activation system was required for mutagenicity only in the positive control ethidium bromide. These results indicate that platinum degradation complexes are weak mutagens which can induce both base pair and frameshift-type mutations. (32 Refs)

23. POTENCY OF SOME CARBAMATES AS MULTIPLE TISSUE SISTER CHROMATID EXCHANGE INDUCERS AND COMPARISON WITH KNOWN CARCINOGENIC ACTIVITIES.

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Cancer Res; 41(11,part1):4489-4492 1981

The ethyl, ethyl N-hydroxy, isopropyl, and methyl esters of carbamic acid were examined for their abilities to induce sister chromatid exchanges (SCEs) in alveolar macrophages, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. The relative potencies in inducing SCE, ethyl greater than ethyl N-hydroxy- greater than isopropyl, paralleled previously described activities for induction of lung adenomas in strain A mice. The noncarcinogenic methyl carbamate was inactive in the SCE assay. Relative to bone marrow, regenerating liver and alveolar macrophage cells demonstrated increased susceptibility to carbamate-induced SCE. Of all carbamates studied, only the directly active compound, ethyl N-hydroxycarbamate, produced distinctly different responses in extrahepatic tissues of hepatectomized and intact mice. In intact mice, SCE levels induced by ethyl carbamate in bone marrow and alveolar macrophage cells were not significantly different whether assay followed the last of 12 (3x weekly) serial injections of 2.2 mmol/kg each or after a single injection of 2.2 mmol/kg. Linear regression relationships of log ethyl carbamate versus log SCE or log adenoma response were found to be parallel with the two assays having similar sensitivities. (Author abstract) (21 Refs)

24. SISTER CHROMATID EXCHANGE (SCE) AND STRUCTURAL CHROMOSOME ABERRATION IN MUTAGENICITY TESTING.

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Hum Genet; 58(3):235-254 1981

An objective analysis is presented of data gained so far relative to the value in mutagenicity testing of sister chromatid exchange (SCE) and classical chromosome aberration (CA) analysis. Detailed studies are reported on spontaneous SCE and chromosome damage in normal cells, and in cells of patients with genetic and neoplastic disease. Qualitative results on SCE induction and CA are presented relative to radiation, chemicals, chromosomal breakage syndromes and virus. Quantitative results are presented on potent inducers of SCE and break aberrations, substances inducing SCE but not breaks in the same test system, and clastogens with no or minor SCE-inducing activity. A section deals with modification of SCE and chromosome breakage: clastogens and anticlastogens. A discussion of molecular aspects of SCE induction and breakage involves consideration of evidence for the primary lesions leading to SCE formation, role of replication and involvement of repair mechanisms. These studies indicate SCE and structural CA are two largely different cytogenetic endpoints of mutagenic action. It is suggested that the SCE-technique is a valuable additional method for cytogenetic testing, which, however, is not adequate to replace the classical methods of analysis of structural chromosome damage. (165 Refs)

25. CARCINOGEN BIOASSAY AND MUTAGE STUDIES WITH THE HYPOLIPIDEMIC AGE GEMFIBROZIL.

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JNCI; 67(5):1105-1116 1981

Gemfibrozil, a novel hypolipidemic agent ide cally as 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid ed for mutagenic potential in in vitro assays w typhimurium. For evaluation of tumorigenic po brozil was administered in the diet (0, 30, and brozil/kg) to groups of noninbred CD-1 mice noninbred CD rats (50/sex) for 78 and 104 wk, r the bacterial mutagenesis assays, between 100 gemfibrozil/plate failed to induce a significant vertant bacterial colonies. Neither was a mutage bacterial assays induced at concentrations up to in vivo metabolites of gemfibrozil isolated from In mice, gemfibrozil did not significantly increa cy or the mean latency period of tumors. In rats, ly significant increases in hepatocellular tumors cell tumors of the testes were dose related. Adr and pancreatic acinar tumors were increased in were inversely dose related. Under the condition gemfibrozil did not elicit a tumorigenic potenti female rats. In male rats and related to the tumor response, the peroxisome proliferation occur in humans chronically administered (Author abstract) (22 Refs)

BINDING OF CARCINOGENS AND METABOLITES TO MACROMOLEC

26. NUCLEAR UPTAKE AND SUBSEQUENT METABOLISM OF BENZO(A)PYRENE BIND CYTOSOLIC PROTEINS.

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Cancer Res; 41(11,part1):4408-4414 1981

The binding of [3H]benzo(a)pyrene to prote cytosol, the nuclear uptake of cytosolic [3H]benzo(a)pyrene, and the subsequent nuclear the polycyclic hydrocarbon were investigated. [3H]benzo(a)pyrene to cytosol had a saturabl component with a Kd of 2.54 nM and a capacit mg protein. Specific binding of [3H]benzo(a)py was also assayed using sucrose density gradien clear uptake of protein-bound [3H]benzo(a)pyre strated both directly and by sucrose density gr The nuclear benzo(a)pyrene was readily conver lites which were qualitatively and quantitative from nuclear metabolites of exogenously (no p ed) added [3H]benzo(a)pyrene. (Author abstract

27. INHIBITION IN VIVO OF THE FORMATION OF ADDUCTS BETWEEN METABOLITES OF BENZO(A)PYRENE AND DNA BY BUTYLATED HYDROXYANISOLE.

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Cancer Res; 41(11,part1):4309-4315 1981

Antioxidants have been shown to inhibit the carcinogenic effects of a variety of chemical carcinogens. For example, the phenolic antioxidant butylated hydroxyanisole (BHA) has been shown to be a potent inhibitor of benzo(a)pyrene (BP)-induced neoplasia in mouse lung and forestomach. The objective of the present study was to determine whether or not BHA, under conditions known to result in inhibition of BP-induced neoplasia, affects the formation of BP metabolite:DNA adducts. Following po administration of a carcinogenic dose of [3H]BP to A/HeJ mice, radioactivity was detected in the DNA of both lung and liver. Analysis of the deoxyribonucleosides by high-pressure liquid chromatography showed that the major adduct in both tissues cochromatographed with the (+-)-7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was 10 to 15% of the BPDEI adduct in both lung and liver. Another adduct, possibly derived from BP phenol(s), was also detected in lung and was 10 to 20% of the BPDEI adduct. Treatment of animals with BHA decreased the amount of the BPDEI adduct in the lung and the liver approx 55 and 75%, respectively. The decrease in the amount of this adduct in the lung appears to correlate with the inhibition of pulmonary adenoma formation. Thus, BHA appears to inhibit BP-induced pulmonary adenoma formation by inhibiting the amount of the BPDE:DNA adducts formed in lung. Possible mechanisms by which BHA treatment inhibits the formation of BPDE:DNA adducts are discussed. (Author abstract) (44 Refs)

28. DOSE-DEPENDENCY OF 2-ACETYLAMINOFLUORENE BINDING TO LIVER DNA AND HEMOGLOBIN IN MICE AND RATS.

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Toxicol Appl Pharmacol; 60(3):472-478 1981

Binding of 2-acetylaminofluorene (2-AAF) to liver DNA and Hb in Sprague-Dawley rats and CD-1 mice of both sexes was determined to test proposals that Hb binding correlates with target organ DNA binding and carcinogenicity. In both species, 2-AAF binding to liver DNA and HB increased as a linear function of dose (1-100 umoles/kg, po). This indicated that the formation of reactive 2-AAF liver metabolites also was linearly related to dose. No sex difference was observed in 2-AAF macromolecular binding, except for an apparent higher liver DNA binding in female mice than in male mice. DNA binding was only 7x greater and Hb binding only 2.5x greater in rats than mice; thus the binding did not reflect the 246x greater carcinogenicity of 2-AAF in rat liver. The results indicated that Hb binding can be used to predict DNA binding and the systemic dose; however, the extent of DNA binding does not predict carcinogenic potency. (20 Refs)

29. ADDUCTS FROM THE REACTION OF O,O'-DIACETYL OR O-ACETYL DERIVATIVES OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE 1-OXIDE WITH PURINE NUCLEOSIDES.

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(c/o Loucheux-Lefebvre) Institut Recherches le Cancer de Lille et Unite, 124 de l'INSERM, BP 311, 59020 Lille Cedex, France

Cancer Res; 41(11,part1):4559-4565 1981

The diacetyl derivative of 4-hydroxyaminoquinoline 1-oxide (4-HAQO), the proximate carcinogen of 4-nitroquinoline 1-oxide, was reacted in vitro with purine nucleosides to give five adducts (3 with guanosine and 2 with adenosine). The same nucleoside modifications were also obtained with a monoacetyl derivative of 4-HAQO which is probably 4-acetoxy-aminoquinoline 1-oxide. The structure of the major adduct (the so-called dG III) was identified as N-(deoxyguanosine-C8-yl)-4-aminoquinoline 1-oxide. The isolation of this adduct from the 4-HAQO-modified DNA in vivo provides strong support for the hypothesis that the acetyl derivatives of 4-HAQO constitute a good model for the ultimate carcinogen. (Author abstract) (21 Refs)

30. ROLES OF 2-HALOETHYLENE OXIDES AND 2-HALOACETALDEHYDES DERIVED FROM VINYL BROMIDE AND VINYL CHLORIDE IN IRREVERSIBLE BINDING TO PROTEIN AND DNA.

Guengerich FP, Mason PS, Stott WT, Fox TR, Watanabe PG
Dept. Biochemistry, Center Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232

Cancer Res; 41(11,part1):4391-4398 1981

The metabolism of [1,2-14C]vinyl bromide (VBR) to products irreversibly bound to DNA and protein was examined in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes. A role for cytochrome P-450 was confirmed using inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VBR metabolism does not appear to be either of the major isozymes induced by phenobarbital or beta-naphthoflavone, as determined by induction, reconstitution, and antibody inhibition studies. 2-Bromoethylene oxide and 2-bromoacetaldehyde, suspected metabolites of VBR, were synthesized and found to be substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. These enzymes were used to probe the roles of the two possible metabolites in the irreversible binding of products of VBR to protein and DNA. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VBR metabolites to protein in microsomal incubations. Epoxide hydrolase was effective in inhibiting the binding of VBR or vinyl chloride metabolites to calf thymus DNA added to such systems, but alcohol dehydrogenase was not. Similar results were obtained for binding of VBR metabolites to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo[1,2-14C]acetaldehyde to protein but not DNA. Binding of vinyl chloride and VBR metabolites to protein was blocked by reduced glutathione, but binding to DNA was not. These results are consistent with the view that 2-haloethylene oxides are the major alkylating agents bound to DNA, and 2-haloacetaldehydes are the major alkylating agents bound to proein in these experimental systems. Studies with labeled 2-bromoacetaldehyde indicate that the slow kinetics of DNA binding by this compound is responsible in part for this phenomenon. Studies with isolated rat hepatocytes suggest that a significant portion of the total and reactive metabolites are able to leave these cells. In these systems, binding of metabolites of vinyl chloride

to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase, implying that, as targets farther away from sources of reactive species are considered, the stabilities of these species become more important for reaction with nucleophilic sites. (Author abstract) (36 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

31. ELLIPTICINES AND HUMAN LIVER MICROSOMES: SPECTRAL INTERACTION WITH CYTOCHROME P-450 AND HYDROXYLATION. INHIBITION OF ARYL HYDROCARBON METABOLISM AND MUTAGENICITY.

Lesca P, Beaune P, Monsarrat B
Laboratoire de Pharmacologie, Toxicologie Fondamentales, 205 route de Narbonne, 31078 Toulouse Cedex, France
Chem Biol Interact; 36(3):299-309 1981

Some pharmacological properties of ellipticine (E) and its derivatives linked to their interaction with cytochrome P-450 have been investigated with human liver microsomes. 9-Hydroxyelipticine (9-OHE) interacts with human liver cytochrome P-450 exhibiting a Type II spectrum (lambdamax:428 nm, Ks = 1.1 uM). After incubation with human liver microsomes the E was converted to 9-OHE; 7-hydroxyellipticine was not produced. The cytotoxic effect of this biotransformation has been evaluated on leukemic L1210 cells, in vitro, and found to be equal to those elicited by liver microsomes of control or phenobarbital (PB) pretreated rats. Moreover, 9-OHE and 9-fluoroellipticine (9-FE) strongly inhibit the benzo[a]pyrene hydroxylase (AHH) activity of human liver microsomes (I50 = 2.6 uM and 1.6 uM, respectively) as well as the mutagenesis induced by the polycyclic aromatic hydrocarbon 2-acetylaminofluorene (AAF); 1 ug/plate of each of these compounds is able to inhibit by more than 50% the mutagenicity of 5 ug/plate AAF. (Author abstract) (29 Refs)

32. DIFFERENTIAL EFFECT OF SEVERAL INDUCERS ON HEPATIC AND MAMMARY BENZO(A)PYRENE METABOLISM IN RAT AND HAMSTER.

Gingell R, Weber A, Ilacqua V, Van de Walle C, Hertzog P
Shell Development Co., Westhollow Res. Center, P. O. Box 822, Houston, TX, 77001
Drug Chem Toxicol; 4(2):101-112 1981

The ability of female Sprague Dawley rat and Syrian golden hamster mammary microsomes, as compared with the liver, to metabolize benzo(a)pyrene (BP) was examined in an attempt to understand the different susceptibilities of these species to polynuclear hydrocarbon-induced mammary tumorigenesis. The effect of pretreatment with several known mixed function oxidase inducers on these activities was studied in both species. Control hamster hepatic benzo(a)pyrene-hydroxylase (BPH) activity was considerably greater than that of the rat. Aroclor was the only inducer to significantly increase hamster hepatic BPH activity, and this by only two-fold. 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene had no effect on hamster liver BPH activity while beta-naphthoflavone (BNF) slightly inhibited this activity. All compounds examined were potent inducers of hepatic BPH and cytochrome P450 in the rat. Control hamster mammary microsomal BPH activity was much lower than the hepatic level, but was four-fold greater than the corresponding level for the rat. All the pretreatments caused similar increases in mammary activity in both species, BNF being the most effective. The ability of control hamster hepatic microsomes to metabolize BP was considerably greater than for the rat. The results indicated that rat and hamster mammary gland microsomes, as well as those of liver, are capable of metabolizing BP. All the pretreatments investigated induced mammary activity in both species, but the rat activity was more inducible than that of the hamster. It was therefore suggested that metabolic activation of carcinogenic polycyclic hydrocarbons can occur in the mammary gland itself. (16 Refs)

33. INDUCTION OF ARYLHYDROCARBON HYDROXYLASE AND BLAST TRANSFORMATION IN HUMAN BLOOD LYMPHOCYTES.

Fukuhara M, Bohuon C, Gharbi N, Biret F, Boudene C
Inst. Public Health, Shirokanedai, Minoto-ku, Tokyo, 108, Japan
Biochem Biophys Res Commun; 102(1):8-14 1981

The induction of arylhydrocarbon hydroxylase (AHH) by benzo(a)pyrene and the degree of blast transformation were measured simultaneously in peripheral hyman lymphocytes. While the induction ratio (induced:basal level) of AHH and induction ratio per unit of blast transformation varied at different culture times and at different phytohemagglutinin (PHA) concentrations for a particular individual, the ratio of absolute induced AHH activity and unit of blast transformation yielded a consistent value at different culture times and different PHA concentrations for the individual. AHH inducibility may be a useful parameter for the study of cancer susceptibility if inducibility is expressed in this new manner. (23 Refs)

34. 1,2-DIMETHYLHYDRAZINE-INDUCED CHANGES IN HEPATIC, SMALL INTESTINAL, AND COLONIC MUCOSAL CYTOCHROMES P-450 AND B5 OF RATS FED CITRUS PULP OR WHEAT BRAN.

Smith-Barbaro P, Hanson D, Reddy BS
Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Drug Metab Dispos; 9(5):487-488 1981

A 3-mo feeding study showed that dietary fiber and the carcinogen 1,2-dimethylhydrazine interacted to alter hepatic and extrahepatic levels of cytochromes P-450 and b5 in liver, and small intestine and colon mucosa of male F344 rats. (16 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

35. CARCINOGEN TESTING: CURRENT PROBLEMS AND NEW APPROACHES.

Weisburger JH, Williams GM
American Health Foundation, Valhalla, NY, 10595
Science; 214(4519):401-407 1981

The classic procedures for testing potential carcinogens in animals have basically not changed in the past 50 yr. Considerable knowledge of the mechanisms of carcinogenesis has accrued in the last 20 yr, particularly concepts on the metabolic activation of chemicals to reactive electrophilic compounds that can interact with nucleophilic cell components including DNA. These developments, in turn, have yielded a framework for integrating into carcinogen testing the determination of genetic effects of chemicals. A systematic decision point approach to carcinogen testing has been developed which entails

a sequential decision-making process as specific tests are performed and evaluated prior to initiation of higher order, more complex tests. Compared to conventional bioassays in rodents, this approach provides knowledge based on mechanisms of carcinogenesis, yields a substantial amount of data at minimal cost, and forms a solid base for eventual health risk assessment. (Author abstract) (34 Refs)

36. NITROSABLE DRUGS.

Ziebarth D
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):587-595 1981

The nitrosation of 61 potentially nitrosable drugs available for po administration in East Germany was studied in vitro under simulated conditions of the human stomach. Nitrosation of 10/61 drugs (aminophenazone, ampicillin, clomipramine, desipramine, ethambutol, imipramine, noramidopyrine methanesulfonate, oxacillin, phenoxymethylpenicillin, and piperazine) was observed. Nitrosodimethylamine, the principal product of aminophenazone, and mononitrosopiperazine, the principal product of piperazine, were identified chemically among the nitrosation products of the drugs. Both metabolites are carcinogenic for several animal species. The nitrosation of 9/10 drugs were inhibited 80-100% by ascorbic acid, and that of ampicillin by 18.2%. The findings indicate that po administered drugs forming carcinogenic N-nitroso compounds should be replaced by non-nitrosable drugs, and other potentially nitrosable drugs should be formulated with ascorbic acid, if they are compatible with this vitamin. (33 Refs) (In GER)

37. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.

Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

A review is presented of the biochemistry and metabolism of inorganic species involved in carcinogenesis. Such species may have a role in transport across the cell membrane, enzymatic and chemical transformation of redox active inorganic species within the cell, coordination to cellular small molecules and macromolecules, and inhibition, activation or change of specificity of cellular enzymes by inorganic species. Oxide complexes are discussed with respect to enzyme interaction, metabolism, and mutagenicity. The role of divalent ions is examined. Oxyanions of V, Cr, Mo, As, and Se cross cell membranes; once inside the cell they may act as phosphate and/or sulfate analogs, inhibiting enzymes which catalyze phosphoryl o r sulfuryl transfer reactions. They may serve as alternate enzyme substrates, but they form ester products which are hydrolytically unstable and decompose readily in aqueous soln. The divalent ions of Be, Mn, Co, Ni, Cd, Hg, and Pb are stable forms which may mimic essential divalent ions such as Mg, Ca, Fe, Cu, or Zn. These ions may complex small molecules, enzymes, and nucleic acids so as to alter the normal activity of these species. Free radicals produced in the presence of these metal ions may damage critical cellular molecules. (216 Refs)

38. CHEMISTRY AND METABOLISM OF METALS RELEVANT TO THEIR CARCINOGENICITY.

Martell AE, Berlin M, Brubaker G, Eichhorn GL, Grotyh D, Jennette K, Petering H, Piscator M, Schubert J, Seven I
Texas A and M Univ., College Station, TX, 77843
Environ Health Perspect; 40:27-34 1981

The chemical reactions of metals leading to cancer are considered. Chemical factors in metal metabolism include oxyanions, thermodynamic effects and kinetic factors that determine speciation, the role of speciation in dose effect-response relationships, and membrane transport. Proposed models of carcinogenesis include direct reactions with DNA and indirect reactions. Directions for future research are recommended. (37 Refs)

39. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

Nickel carcinogenesis research since 1975 is reviewed, with emphasis on new experimental techniques for studying carcinogenesis in vivo and in vitro. The subjects covered include epidemiologic studies, clinical investigations, carcinogenicity tests in animals exposed to nickel compounds by different administration routes, x-ray diffractometry and radiotracer studies of alpha-Ni3S2 metabolism, electron microscope studies of alpha-Ni3S2-induced tumors, cytogenetic and tumor transplantation studies, effects of nickel compounds on DNA synthesis, cell culture studies, bacterial mutagenicity tests, and effects of metals on viral and bacterial DNA polymerase. Prospects for future research on nickel carcinogenesis are summarized. (82 Refs)

40. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.

Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

Subcellular systems that influence ultimate cellular responses to toxic and carcinogenic metals are reviewed. They include the endoplasmic reticulum (microsomal enzyme systems and protein synthesis), nuclei, mitochondria, lysosomes, and cellular membranes. Cell membranes regulate carcinogen uptake; microsomal enzymes are responsible for carcinogen metabolism; mitochondria and lysosomes c an affect detoxification and storage of carcinogens; and nuclear DNA polymerases can repair carcinogen-induced damage. (102 Refs)

41. HISTORY OF CANCER INVESTIGATION.

Gomez P, Rosado A
Unidad de Investigacion Clinica, Centro Medico Nacional, IMSS, Av. Cuauhtemoc 330, Mexico 7, D.F., Mexico
Arch Invest Med (Mex); 12(3):361-375 1981

Important biological hypotheses of carcinogenesis are reviewed: the majority are concerned with alterations in cellular genetic material. Chemical, physical, and viral carcinogens and their actions on cell metabolism are presented. Carcinogenesis occurs through somatic mutation resulting from external and internal factors. Solving the cancer riddle depends on advances in molecular biology and genetics with respect to regulatory

mechanisms of cell differentiation and genetic control of differentiated cells. (49 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/11

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
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9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
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Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
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12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

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17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
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18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
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23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

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28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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MECHANISMS OF CARCINOGENESIS

Activation and Metabolism of Carcinogens

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. CALCULATION OF REACTIVITY INDICES FOR BENZ(A)ANTHRACENE AND BENZO(A)PYRENE AND THEIR APPROXIMATIVE MODELS OF COMPLEX WITH ENZYME EPOXIDASE.

Miertus S, Majek P
Inst. Polymers, Slovak Acad. Sciences, 809 34 Bratislava, Czechoslovakia
Neoplasma; 28(4):441-446 1981

By theoretical methods of quantum mechanics an interaction between carcinogenic hydrocarbons - benz(a)anthracene, benz(a)pyrene - and various groups simulating an effect of enzyme oxidase has been studied. If accord is to be achieved with formation of epoxides of these compounds in vivo according to the bay region theory (ie, in A region) an interaction between the enzyme involving an electron-acceptor group and the bay region of hydrocarbon under simultaneous steric hindrance of the K region is necessary. Another possibility of obtaining the highest reactivity in the A region is to assume the formation of the radical cation as a first intermediate in the interaction with enzyme. (Author abstract) (9 Refs)

2. SLOWER STEP OF THE POLYCYCLIC AROMATIC HYDROCARBONS METABOLISM: KINETIC DATA FROM MICROSPECTROFLUOROMETRIC TECHNIQUES.

Salmon J-M, Thierry C, Serrou B, Viallet P
(c/o Serrou), Laboratoire d'Immunopharmacologie des Tumeurs, FRA-INSERM, B. P. 5054, 34033 Montpellier, France
Biomedicine; 34(4):102-107 1981

A microspectrofluorometer has been used for kinetic studies of the decrease of benzo(a)pyrene and benzo(k)fluoranthene fluorescence. This decrease is observed for single living cells: L cells and human peripheral blood monocytes, after their incubation with culture medium containing these compounds and washing the petri dish with fresh medium. The entire fluorescence spectra is recorded at given time intervals in order to watch at some eventual spectral modification. The fluorescence decrease is monoexponential and its parameters are computed with a program based on the least squares fit method. Such determination shows no difference between the calculated rate constants of metabolization for B(a)P and B(k)F and, as long as we consider L cells with a similar morphological shape, only statistical fluctuations of the rate constants of metabolism are observed. As compared, monocytes show faster kinetics of the decrease of the B(a)P intracellular fluorescence due to B(a)P metabolism, and also a more reached dispersion of the values of the rate constant than the one observed for L cells indicating some heterogeneity in the monocyte population of each donor. (Author abstract) (13 Refs)

3. ALPHA-HYDROXYLATION PATHWAY IN THE IN VITRO METABOLISM OF CARCINOGENIC NITROSAMINES: N-NITROSODIMETHYLAMINE AND N-NITROSO-N-METHYLANILINE.

Kroeger-Koepke MB, Koepke SR, McClusky GA, Magee PN, Michejda CJ
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(10):6489-6493 1981

Evolution of 15N2-labeled molecular nitrogen was used to gauge the extent of alpha-hydroxylation during rat liver homogenate metabolism of doubly 15N-labeled N-nitrosodimethylamine (DMN) and N-nitrosomethylaniline (NMA). These measurements were correlated with the extent of total metabolism as measured by the disappearance of nitrosamines and by the formation of formaldehyde. The results indicate that approx 34% of DMN and 19% of NMA were metabolized by the alpha-hydroxylation pathway. Positive controls utilizing doubly 15-labeled N-nitroso-N-methylurea yielded 96% of labeled nitrogen. These results are in variance with previously published data which claimed that either less than 5% or about 100% of DMN is metabolized by the route in vitro. Formaldehyde formation was shown to be a poor measure of the extent of metabolism. Semicarbazide gave rise to both formaldehyde and nitrogen, which makes it an undesirable component of the in vitro metabolism mixtures, particularly when those two substances are being measured. (Author abstract) (32 Refs)

4. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE (MEETING ABSTRACT).

Hecht SS, Young R, Chen CB
American Health Foundation, Valhalla, NY, 10595
Toxicologist; 1(1):35 1981

N-Nitrosomorpholine (NM) is a potent carcinogen which induces liver tumors in rats and tumors of the trachea and nasal cavity in Syrian golden hamsters. 3,3,5,5-TetradeuteroNM is less carcinogenic and less mutagenic than NM, indicating that the metabolic activation of NM proceeds by hydroxylation of the 3 and 5 carbons (alpha carbons). However, metabolic alpha hydroxylation of NM has not been previously demonstrated. We incubated NM with rat liver microsomes and an NADPH generating system and demonstrated alpha hydroxylation by isolation of (2-hydroxyethoxy)acetaldehyde as its 2,4-dinitrophenylhydrazone (DNP) derivative. The rate of formation of (2-hydroxyethoxy)acetaldehyde in microsomal incubation mixtures can be assayed by reverse-phase high pressure liquid chromatography (HPLC) of its DNP. When rats were injected with NM, we did not detect (2-hydroxyethoxy)acetaldehyde in the urine, but we did isolate (2-hydroxyethoxy)acetic acid, which presumably resulted from further oxidation. Data will be presented on the deuterium isotope effect for alpha hydroxylation of NM and on the effects of mixed function oxidase inducers on alpha hydroxylation. (no Refs)

5. METABOLIC ALPHA-HYDROXYLATION OF N-NITROSOMORPHOLINE AND 3,3,5,5-TETRADEUTERO-N-NITROSOMORPHOLINE IN THE F344 RAT.

Hecht SS, Young R
Div. Chemical Carcinogenesis, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Cancer Res; 41(12):5039-5043 1981

We studied the metabolism in the male F344 rat of N-nitrosomorpholine and of 3,3,5,5-tetradeutero-N-nitrosomorpholine; the latter is less carcinogenic and less mutagenic than is N-nitrosomorpholine. Alpha-Hydroxylation (3-or 5-hydroxylation) of N-nitrosomorpholine by liver microsomes and a reduced nicotinamide adenine dinucleotide phosphate-generating system produced (2-hydroxyethoxy)acetaldehyde, which was identified as its 2,4-dinitrophenylhydrazone derivative. When we administered N-nitrosomorpholine to rats ip, we did not detect (2-hydroxyethyl)a cetaldehyde in the urine, but we did identify (2-hydroxyethoxy)acetic acid (16% of the dose). We also identified N-nitroso(2-hydroxyethyl)glycine (33% of the dose) from beta-hydroxylation (2-or 6-hydroxylation), N-nitroso-diethanolamine (12%), and unchanged N-nitrosomorpholine (1.5%) in

the urine. The deuterated analogs of the above metabolites were isolated from the urine of rats treated with 3,3,5,5-tetradeutero-N-nitrosomorpholine in yields as follows: (2-hydroxyethoxy)acetic acid (3.4%); N-nitroso(2-hydroxyethyl)glycine (37%); N-nitrosodiethanolamine (12%); N-nitrosomorpholine (0.4%). These data demonstrate that deuterium substitution in the alpha-positions of N-nitrosomorpholine caused a decrease in the extent of alpha-hydroxylation and indicate that alpha-hydroxylation is the mechanism of activation of N-nitrosomorpholine. (Author abstract) (31 Refs)

6. METABOLISM OF NITROSOACETOXYMETHYLMETHYLAMINE IN LIVER MICROSOMES.

Appel KE, Frank N, Wiessler M

Dept. Toxicology, Inst. Pharmacology, Obere Zahlbacher Str. 67, D-6500 Mainz, W. Germany

Biochem Pharmacol; 30(20):2767-2772 1981

The carcinogen nitrosoacetoxymethylmethylamine (NAMM) was incubated with mouse liver microsomes. The decomposition rate of NAMM and the formation of methanol were determined. After addition of an NADPH-regenerating system, formaldehyde formation resulting from metabolic degradation of the methyl group of NAMM was measured. The results suggest that NAMM is rapidly hydrolyzed by unspecific esterases to nitrosohydroxymethylmethylamine (NHMM). NHMM decomposes according to the activation mechanism of nitrosodimethylamine (NDMA). The formation of methanol proceeds with an even lower velocity. This indicates that intermediate breakdown products - probably NHMM or methyldiazohydroxide (MDH) - possess a distinct stability. Oxidative demethylation of NHMM or MDH was not detectable. The methanol formed is oxidized to formaldehyde by microsomal enzymes. (Author abstract) (31 Refs)

7. METABOLIC FATE OF N-METHYL-N-DODECYLNITROSAMINE IN THE RAT, IN RELATION TO ITS CARCINOGENICITY TO THE URINARY BLADDER.

Suzuki E, Mochizuki M, Okada M

Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Gan; 72(5):713-716 1981

The metabolic fate of N-methyl-N-dodecylnitrosamine (MDN) was investigated in the rat, in order to elucidate a possible correlation between urinary metabolites and organotropic carcinogenicity to the urinary bladder of this N-nitrosamine. MDN was extensively metabolized in the rat, no unchanged MDN being found in the urine. The urinary metabolites identified were N-methyl-N-(3 carboxypropyl)nitrosamine (MCPN), N-methyl-N-(2-hydroxy-3-carboxypropyl)nitrosamine, N-methyl-N-(carboxymethyl)nitrosamine, and N-methyl-N-(2-oxopropyl)nitrosamine. Thus the metabolic pattern of MDN was essen tially similar to that of N-methyl-N-(4-hydroxybutyl)nitrosamine, a potent bladder carcinogen, in the rat. A possible important role of MCPN in the induction of bladder tumors by MDN is discussed. (Author abstract) (21 Refs)

8. COMPREHENSIVE ANALYSIS OF URINARY METABOLITES OF N'-NITROSONORNICOTINE.

Hecht SS, Lin D, Chen CB

Div. Chemical Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Carcinogenesis; 2(9):833-838 1981

Urinary N'-nitrosonornicotine (NNN) metabolites in male F-344 rats, male Syrian golden hamsters, and male A/J mice were quantified by high-pressure liquid chromatography. In F-344 rats injected with NNN (3-300 mg/kg), the main urinary products were hydroxy acid (37.2-53.3% of the administered dose), NNN-1-oxide (6.7%-10.7%), norcotinine (3.2-5.1%), keto acid (31.1%-12.8%), and NNN (3.3%-5.2%). Despite the differing organ specificity of NNN in the three species, urinary metabolites in mice and hamsters were qualitatively similar to those in rats. In each case, a marked capacity for 2'- and 5'-hydroxylation was observed. The in vivo metabolites resulting from 2'-hydroxylation of NNN by rat liver microsomes were myosmine and keto alcohol; both gave rise to keto acid as the major urinary metabolite. Lactol, the product of microsomal 5'-hydroxylation, gave hydroxy acid as its major urinary metabolite. The two major metabolites are probably reliable indicators of NNN alpha-hydroxylation in vivo. (19 Refs)

9. THE ORGAN CULTURE OF RAT ESOPHAGEAL MUCOSAL EPITHELIUM AND ITS RESPONSE TO N'-NITROSONORNICOTINE (MEETING ABSTRACT).

Reiss B, Hecht SS, Williams GM

Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595

In Vitro; 17(3):223 1981

Using techniques similar to those beneficial for the prolonged organ culture of rodent colon, we have maintained rodent esophagus for up to 35 days. During this interval, the normal architecture and histology of the mucosal epithelium were preserved, and normal cell proliferation and keratinization were retained. Kinetic studies of cells labelled during DNA synthesis demonstrated a continuation of epithelial cell maturation and migration for at least 4 wk. Exposure to the model esophageal carcinogen, N'-nitrosonornicotine (NNN; 10(-2) M) for 48 hr in culture suppressed DNA synthesis of conventional rat esophageal mucosa at 2 days; higher incorporation than controls occurred at 1, 2 and 3 wk. Exposure to 14C-NNN for 48 hr resulted in the formation of 4-oxo-4-(3-pyridyl)butyric acid from 2'-hydroxylation and 4-hydroxy-4-(3-pyridyl)butyric acid from 5'-hydroxylation of NNN. The levels of these metabolites indicated that, unlike the hepatic metabolism of NNN, the extent of 2'-hydroxylation in the esophagus exceeds that of 5'-hydroxylation. These results may provide the metabolic basis for the organo-s electivity of NNN. Fragments of organ-cultured esophagus implanted into mammary fat pads of syngeneic animals have been maintained for up to 6 mo. Fragments exposed to NNN for 48 hr and then implanted developed a hyperplastic mucosal epithelium after 2 mo in the host. This potentially preneoplastic change was not observed in controls. (1 Ref)

10. THE EFFECT OF THE PANCREATIC CARCINOGEN N-NITROSO-2-METHOXY-2,6,-DIMETHYL-MORPHOLINE ON ENDOCRINE AND EXOCRINE PANCREAS OF SYRIAN HAMSTERS (MEETING ABSTRACT).

Pour PM
The Eppley Institute for Research in Cancer, Omaha, NE
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

All nitrosamines with a pancreatic carcinogenic effect of Syrian hamsters have a common metabolite, N-nitroso(-2-hydroxypropyl) (2-oxopropyl)amine (HPOP). As the cyclic structure of this metabolite, resembling the pyranose form of the hexose-sugars and the sugar moeity of the Streptozocin (SZ), may be responsible for its affinity for the pancreas, we studied the effect of N-nitroso-2-methoxy-2,6-dimethyl nitrosomorpholine (MeNDNM), a fixed cyclic form of HPOP. We found that a single high dose of this compound exhibited, compared to the effect of SZ, selective necrosis of the B-cells of pancreatic islets within 3 days. In surviving hamsters the islets showed signs of regeneration, which was completed within 60-72 hr. Some 40 wk later, however, and in contrast to the effect of SZ, almost all treated hamsters developed pancreatic ductular and mixed ductular-insular tumors. On the other hand, weekly application of MeNDNM in subdiabetogenic induced equivalent tumors, but did not appear to affect islet cells. These results point to the mutual response of the endocrine and exocrine pancreas to this compound, thus indicating the importance of the carcinogen's cyclic structure. Possible mechanisms involved in pancreatotropic effects of this class of chemical carcinogens will be discussed. (no Refs)

11. RELATIONSHIP OF RAT URINARY METABOLITES OF N-NITROSOMETHYL-N-ALKYLAMINE TO BLADDER CARCINOGENESIS.

Singer GM, Lijinsky W, Buettner L, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(12):4942-4946 1981

Nitrosomethylalkylamines with chain lengths from C4 (n-butyl-) to C14 (n-tetradecyl-) were each administered to three rats at doses equimolar with 12 mg of the butyl compound. All of the compounds administered to rats at this dose, twice a wk for 30 wk, induced tumors in 100% of the animals. Some of the compounds with even-numbered alkyl chains induced bladder tumors, and a connection was sought with the metabolites of these excreted in urine. The pooled 24-hr urine was extracted with ethyl acetate before and after acidification to provide a neutral fraction and a fraction containing nitrosamino acids. The fraction containing the acids was analyzed by capillary gas chromatography and by gas chromatography-mass spectrometry after esterification with diazomethane; the neutral fraction was analyzed similarly. The principal metabolite of the nitrosamines with odd-numbered chains was found in the acidic fraction and was identified as nitrosomethyl-2-carboxyethylamine. There were several acids in the mixtures derived from the nitrosamines with even-numbered chains, nitrososarcosine and nitrosomethyl-3-carboxypropylamine being the major components. There was no trend in the yields of the nitrosamino acids that could be correlated with the differences in carcinogenic potency between the nitrosamines; the max yield of acids was more than 30% (from the tetradecyl compound). The principal component of the neutral fraction (+-1% of the nitrosomethylalkylamine administered) was nitrosomethyl-2-oxopropylamine. The yield of this compound increased with increasing length of the even-numbered chain nitrosamines. (Author abstract) (14 Refs)

12. THE CHEMISTRY OF ACTIVATED INTERMEDIATES OF N-NITROSO COMPOUNDS CONTAINING THE 2-OXOPROPYL GROUP (MEETING ABSTRACT).

Nagel D, Wallcave L, Mirvish S, Smith J
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Newsletter Natl Pancreas Cancer Project; VI(2):43 1981

To date all N-nitrosamines which contain or are metabolized to nitrosamines containing a 2-oxopropyl group have been shown to induce pancreatic adenocarinoma in the Syrian hamster. Within this series of nitrosamines bis(2-oxopropyl)nitrosamine (BOP) is the most specific for the hamster pancreas while methyl-2-oxopropyl-nitrosamine (MOP) is the most potent (MOP induces tumors in the hamster pancreas and other organs with a single dose of 2.5 mg/kg). In vivo alkylation studies have shown that BOP predominantly methylates pancreatic DNA while liver DNA is both methylated and alkylated with a longer alkyl group of unknown nature (perhaps a 2-oxopropyl group). Two mechanisms of activation of BOP appear plausible. (1) BOP is metabolized to MOP which in turn is alpha hydroxylated yielding either a methylating on 2-oxopropylating species which can react with cellular macromolecules including DNA, producing methylated or oxopropylated adducts. 2) Alternatively BOP is alpha hydroxylated and decomposes by two different routes. The classical decomposition pathway would lead to a 2-oxopropylating species while a second competing pathway would lead to a methylating species. To test these hypotheses we have prepared ethyl-N-nitroso-2-oxopropylcarbamate (OPC) and the two alpha acetoxy derivatives of MOP [N-acetoxymethyl-N-2-oxopropylnitrosamine (AMOP) and N-methyl-N-(1-acetoxy-2-oxopropyl)amine (MAOP)] and studied their soln chemistry and reactions with selected nucleophiles. OPC reacts with 3,4-dichlorothiophenol producing both methylated and oxopropylated thioethers supporting the second hypothesis while the extreme reactivity of MAOP in solvolysis studies in comparison to alpha-acetoxydimethylnitrosamine tends to support the first hypothesis. (no Refs)

13. THE FORMATION OF N-NITROSOMETHYL(2-OXOPROPYL)AMINE FROM N-NITROSOBIS(2-OXOPROPYL)AMINE IN VIVO.

Lawson TA, Helgeson AS, Grandjean CJ, Wallcave L, Nagel D
Eppley Inst. Res. Cancer 0613, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105
Carcinogenesis; 2(9):845-849 1981

Tissue concentrations of N-nitrosobis(2-oxopropyl)amine (BOP) and its metabolites in male Syrian golden hamsters given a single dose of BOP (10 mg/kg, sc) were analyzed by gas chromaography. BOP concentrations were higher in the pancreas than in the liver or salivary glands. N-nitrosomethyl(2-oxopropyl)amine (MOP) was present in higher concentrations in the pancreas than in the liver, and N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine also was preferentially taken up by the pancreas. The results strongly suggested that MOP is a proximate carcinogenic metabolite of BOP. (15 Refs)

14. PEROXIDASE ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS (MEETING ABSTRACT).

Wong PK, Hampton MJ, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Rat mammary gland parenchymal cells activate N-hydroxy-2-acetylaminofluorene (N-OH-AAF) to 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAC-AAF) via a nitroxyl free radical form of the carcinogen. Prostaglandin synthetase has a peroxidase activity and hence we have examined parenchymal cells to determine if the activation of N-OH-AAF in the cells occurs by this route. Freshly isolated cells activate N-OH-AAF to NOF as detected by high pressure liquid chromatography (HPLC). Cells frozen at-60C are more active. N-OH-AAF activation appears to be peroxidative since ascorbate and p-aminophenol completely inhibit NOF formation. Neither the acyl-transferase nor deacylase route occurs to any appreciable extent in the cells. Exogenously added arachidonate enhances N-OH-AAF activation and the inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) considerably decreased N-OH-AAF activation while indomethacin or aspirin were not effective. Ram seminal vesicle microsomes activate N-OH-AAF apparently by prostaglandin synthetase. Our work indicates that N-OH-AAF was activated by lipoxygenase pathway in these cells. The 12L-hydroperoxy-5,8,10,14-icosatetraenoic acid (12-HPETE) generated through endogenous or exogenous arachidonate sources probably is the hydroperoxide substrate for the peroxidase. Platelets which are rich in lipoxygenase also activate N-OH-AAF. Since 12-HPETE is one of the three hydroperoxides found in animal kingdom, the peroxidase activation may have significant importance in mammary gland carcinogenesis. (no Refs)

15. METABOLISM AND DISPOSITION OF TRIS BP IN THE RAT (MEETING ABSTRACT).

Matthews HB, Nomeir AA
National Institute of Environmental Health Science and National, Toxicology Program Research Triangle Park, NC, 27709
Toxicologist; 1(1):35 1981

The flame retardant chemical tris (2,3-dibromopropyl)phosphate (Tris BP), has been shown to be carcinogenic in laboratory animals. In an effort to provide additional data on the disposition of Tris BP in laboratory animals the oral and dermal absorption, tissue distribution, metabolism and excretion of 14C-labeled Tris BP have been studied in the rat. The results of these studies indicate that Tris BP is readily absorbed from the gastrointestinal tract and absorbed at an appreciable rate from the skin. Following absorption Tris BP is distributed to all the major tissues, but Tris BP derived radioactivity is most concentrated in liver, blood and kidney. Tris BP is readily metabolized and excreted in the form of several polar metabolites in urine and feces and as CO2 in exhaled air. Six metabolites of Tris BP have been isolated and identified from urine and bile. Excretion of unmetabolized Tris BP is negligible. In vitro studies of Tris BP metabolism have demonstrated that enzymes in liver degrade the parent chemical to the same polar metabolites which were isolated and identified from urine and bile. The enzymes responsible for Tris BP metabolism are concentrated in microsomal and soluble portions of liver homogenates and require NADPH and glutathione, respectively, as cofactors for enzyme activity. (no Refs)

OTHER METABOLISM OF CARCI

16. EFFECTS OF CARCINOGENS, MUTAG TERATOGENS ON NON-HUMAN SPECIE ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP
United States Environmental Protection Agency, (
Second Annual NCI/EPA/NIOSH Collaborative on Joint Environmental and Occupational Can ber 9-11, 1981, Rockville, Maryland. National pp., 1981.

Aquatic systems and organisms are unde and field study in order to develop indicat modeling capabilities for detection and eval carcinogens, mutagens, and teratogens. In th program, several advances were made in th minnow (liver lesions via benzidine and afl rainbow trout (liver tumors via benzo(a)pyr sures), and freshwater catfish (papillomatou chlorinated effluent exposures). A novel app that tiger salamanders may be good biochemi indicators of the presence of certain carcin aromatic hydrocarbons-PAH's). The skin an the salamanders revealed induced enzyme exposure to the PAH, perylene. Considerabl work on mollusks and carcinogenic PAH's Oregon has revealed a positive correlation be of cellular proliferation disorders in shellfish centrations of certain PAH's in natural water chemistry for the last yr has been directed elucidation of the metabolisms of the mixed in marine organisms. From continuing wo (Mugil cephalus), we have found that benzo verted mainly to 3-hydroxybenzo hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-d B(a)P, in in vitro systems containing liver Aroclor 1254-treated mullet. Other metaboli of B(a)P and probably tri- and tetraols hav duced. We have also developed a procedur hydrolase enzyme system in order to determi enzyme on the metabolism of the polyaroma These studies continue to reveal that fish hav ic pathways to mammals for disposition of ce (no Refs)

17. URINARY METABOLITES OF N-NITROSODIPROPYLAMINE, N-NITROSO HYDROXYPROPYLPROPYLAMINE AND OXOPROPYLPROPYLAMINE IN THE RA

Leung KH, Archer MC
(c/o Archer) Dept. Medical Biophysics, Univ Cancer Inst., 500 Sherbourne St., Toronto, Can
Carcinogenesis; 2(9):859-862 1981

Male Sprague-Dawley rats in groups of were inoculated ip with N-nitrosodipropyla mg/kg), N-nitroso-2-hydroxypropylpropylam mg/kg), or N-nitroso-2-oxopropylpropylami mg/kg). In each case, the major urinary m beta-glucuronide of NHPPA. Exhaustive hy urine samples with beta-glucuronidase yi NHPPA in amounts corresponding to 5%, the administered doses of NDPA, NHPPA, spectively. Levels of unchanged nitrosamines lites (NHPPA for administered NDPA or N

erally low: less than 2% of the administered dose). N-nitrosomethylpropylamine and N-nitrosodimethylamine were not detected in any urine samples. (22 Refs)

18. ENTEROHEPATIC FATE OF AFLATOXIN B1 (MEETING ABSTRACT).

Wong JJ, Kayashima L, Hsieh PH
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):33 1981

Previous metabolic research on the potent food-borne carcinogen, aflatoxin B1 (AFB1) has primarily focused upon the liver and only speculated upon its interrelationship with the gastroint estinal tract in AFB1 disposition and toxicity. Using in situ metabolism techniques, male Sprague-Dawley rats received intestinal doses of 14C-AFB1 equivalent to that calculated for 24 hr dietary exposure to 1ppm AFB1. Curve-fit estimates of AFB1 absorption indicates that the total hepatic exposure to AFB1 would equal approx 5 ug or 27% of dose within 24 hr. Intraportal injection of less than 4 ug of AFB1 indicates that excretion in the bile begins within 10 min. Estimates indicate that within 24 hr approx 64% of dose would be excreted in the bile. High pressure liquid chromatography and thin layer chromatography analysis of the bile failed to detect AFB1 or any of its known metabolites. Preliminary Ames mutagen tests have not detected any bile-borne mutagenic activity. Venous blood sampled from the inferior vena cava revealed a concentration of less than 1.0% of dose/ml blood. Approx 40% of this amount was bound to blood proteins, 30% associated with aqueous phase, and no 'free' AFB1 detected. Re-injection of bile into the small intestine did not result in detectable reabsorption. Evidence indicates that during chronic dietary exposure to AFB1, the liver is capable of substantial first-pass extraction and efficient biliary elimination of AFB1 metabolites. Biliary-borne metabolites appear to represent detoxification products and not subject to enterohepatic recirculation. (no Refs)

19. THE METABOLISM AND EXCRETION OF STYRENE OXIDE-GLUTATHIONE CONJUGATES IN THE RAT AND BY ISOLATED PERFUSED LIVER, LUNG AND KIDNEY PERFUSIONS.

Steele JW, Yagen B, Hernandez O, Cox RH, Smith BR, Bend JR
(c/o Bend) Lab. Pharmacology, NIEHS/NIH, P.O. Box 12233, Research Triangle Park, NC, 27709
J Pharmacol Exp Ther; 219(1):35-41 1981

The metabolism and excretion of styrene oxide (SO)-glutathione conjugates (SO-GSH) were studied in the intact rat by isolated perfusion techniques in rat lung, liver and kidney. Styrene, or its metabolite, SO, constitutes a potential biohazard, since the latter is a known mutagen. The experiments demonstrated that the rat is capable of rapid conversion of SO-GSH to various derivative metabolites, and of rapid excretion of all SO thioether conjugates. (22 Refs)

20. MOLECULAR MECHANISMS INVOLVED IN THE BLADDER TOXICITY OF SODIUM ORTHOPHENYLPHENOL (SOPP) (MEETING ABSTRACT).

Reitz RH, Fox TR, Quast JF, Hermann EA, Watanabe PG
Dow Chemical, Midland, MI
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

SOPP has been reported to increase urinary tumors in rats. However, OPP (free base) and SOPP failed to produce mutations in 5 strains of Salmonella typhimurium and SOPP did not induce unscheduled DNA synthesis in rat hepatocytes. DNA alkylation was not detected after gavage with 500 mg/kg of OPP or SOPP. These studies suggest little or no genotoxicity for these materials. Animals consuming diets with 2 percent OPP or SOPP were sacrificed after 3, 7, 14, 30, and 90 days. Progressive hyperplasia of bladder epithelium was noted in the SOPP group, but was absent in the OPP group. Focal kidney lesions were observed in the OPP group, but were largely absent in the SOPP group. The metabolism of both OPP and SOPP was dose dependent. Below 150 mg/kg, 90-97 percent of the urinary metabolites were identified as sulfate and glucuronide conjugates, with 3-6 percent oxidation products apparently derived from microsomal (MFO) pathways. Following 500 mg/kg (gavage) or dietary administration (2 percent) or OPP and SOPP, 20-30 percent of the urinary metabolites were oxidation products. Thus, the production of reactive MFO metabolites may be correlated with the bladder toxicity observed in rats consuming diets containing high levels of SOPP but not observed after low levels of SOPP. The lack of genotoxicity of OPP and SOPP coupled with the dose dependent production of an oxidative metabolite suggests that the toxicity and carcinogenicity may be manifest only at high metabolically saturating doses. (1 Ref)

MODIFICATION OF CARCINOGEN METABOLISM

21. SPECIFICITY IN THE ACTIVATION AND INHIBITION BY FLAVONOIDS OF BENZO[A]PYRENE HYDROXYLATION BY CYTOCHROME P-450 ISOZYMES FROM RABBIT LIVER MICROSOMES.

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J Biol Chem; 256(21):10897-10901 1981

The effect of flavone and 7,8-benzoflavone on the metabolism of benzo[a]pyrene to fluorescent phenols by five cytochrome P-450 isozymes obtained from rabbit liver microsomes was determined. Benzo[a]pyrene metabolism was stimulated more than five-fold by the addition of 600 uM flavone to a reconstituted monooxygenase system consisting of NADPH, cytochrome P-450 reductase, dilauroylphosphatidylcholine, and cytochrome P-450LM3c or cytochrome P-450LM4. In contrast, an inhibitory effect of flavone on benzo[a]pyrene metabolism was observed when cytochrome P-450LM2, cytochrome P-450LM3b, or cytochrome P-450LM6 was used in the reconstituted system. 7,8-Benzoflavone (50-100 uM) stimulated benzo[a]pyrene metabolism by the reconstituted monooxygenase system about 10-fold when cytochrome P-450LM3c was

used, but benzo[a]pyrene hydroxylation was strongly inhibited when 7,8-benzoflavone was added to the cytochrome P-450LM6-dependent system. Smaller effects of 7,8-benzoflavone were observed on the metabolism of benzo[a]pyrene by the cytochrome P-450LM2-, cytochrome P-450LM3b-, and cytochrome P-450LM4-dependent monooxygenase systems. These results demonstrate that the activating and inhibiting effects of flavone and 7,8-benzoflavone on benzo[a]pyr ene metabolism depend on the type of cytochrome P-450 used in the reconstituted monooxygenase system. (Author abstract) (44 Refs)

22. METABOLISM OF BENZO(A)PYRENE BY BRAIN MICROSOMES OF FETAL AND ADULT RATS AND MICE. INDUCTION BY 5,6-BENZOFLAVONE, COMPARISON WITH LIVER AND LUNG MICROSOMAL ACTIVITIES.

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Carcinogenesis; 2(9):919-926 1981

Pregnant C57Bl/6 mice and WAG rats were injected ip with 5,6-benzoflavone (BF). On day 19 of gestation the animals were sacrificed, and fetal and maternal brain, lung, and liver microsomes were incubated with benzo(a)pyrene (BP). Liver microsomes of pregnant female mice were only slightly inducible compared with 10x and 4x control level induction of brain and lung microsomes. A 40x, 2x, and 16x control induction by BF was observed for fetal microsomes from the liver, brain, and lung, respectively. In rats, BP metabolism by brain microsomes was greater than that by lung microsomes. (44 Refs)

23. THE METABOLISM OF BENZO(A)PYRENE IN TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLAST CELL LINES.

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Diss Abstr Int [B]; 42(3):913-B 1981

Incubation of benzo(a)pyrene (BaP) with intact C3H/10T1/2 cells for 48 hr resulted in the conversion of this carcinogen to organic-soluble derivatives, which cochromatographed with benzo(a)pyrene-7,8-dihydrodiol, benzo(a)pyrene-9,10-dihydrodiol, and 3-and 9-hydroxybenzo(a)pyrene, and to water-soluble derivatives. The metabolic activation of BaP was studied by testing a comprehensive series of 9 BaP metabolites for their ability to transform C3H/10T1/2 cells. Of all the derivatives examined, only (+/-) benzo(a)pyrene-7,8-dihydrodiol was as active as the parent hydrocarbon in the production of oncogenic transformation. In addition, the major DNA-binding species produced in BaP-treated C3H/10T1/2 cells was identified as benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide. These results strongly support current proposals that benzo(a)pyrene-7,8-dihydrodiol and benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide are the proximal and ultimate carcinogenic forms of BaP. The basis for cellular susceptibility to oncogenic transformation was investigated by comparing the metabolism of BaP by CVP3SC6 (CVP) cells, which are not responsive to BaP-induced transformation, and by C3H/10T1/2 cells. Although CVP cell microsomes were not as active as C3H/10T1/2 cell microsomes in the metabolism of BaP, its metabolism by intact CVP and C3H/10T1/2 cells was quantitatively and qualitatively very similar. CVP cells could be transformed by BaP treatment plus exposure to the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). CVP cells tr eated with BaP plus TPA exhibited both morphological alterations and a loss of anchorage dependence. These studies emphasize that not only metabolic activation leading to DNA adduct formation and mutagenesis, but also the ability to express carcinogen-induced damage play an important role in determining cellular susceptibility to carcinogenesis. (no Refs)

24. METABOLISM OF BENZO[A]PYRENE IN RAT PROSTATE GLANDS FOLLOWING 2,3,7,8-TETRACHORODIBENZO-P-DIOXIN EXPOSURE.

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Carcinogenesis; 2(9):823-831 1981

Benzo(a)pyrene (BP) metabolism was studied in the prostate glands of adult Sprague-Dawley rats treated with the potent monooxygenase inducer 2,3,7,8-tetrachorodibenzo-p-dioxin (TCDD: 2.5, 5, or 10 ug/kg, po). TCDD not only caused selective induction of prostatic aryl hydrocarbon hydroxylase (AHH) and cytochrome P-446, but also resulted in a significant increase in organic-soluble BP metabolites over aqueous conjugated metabolites. High-pressure liquid chromatography analysis showed that formation rates of phenols, quinones, and dihydrodiols in TCDD-induced prostate glands were, respectively, 290, 192, and 38 times higher than in noninduced glands. The rate of 7,8-diol formation was 1.5 times that of 4,5-diol and 3 times that of 9,10 diol. TCDD-induced increases in BP metabolites were dose dependent, and they coincided with the magnitude of AHH induction The possibility that increased 7,8-diol synthesis could lead to increased synthesis of the ultimate BP carcinogen and prostate tumor induction is discussed. (30 Refs)

25. COMPARISON OF THE PROMOTING ACTIVITY OF PRISTANE AND N-ALKANES IN SKIN CARCINOGENESIS WITH THEIR PHYSICAL EFFECTS ON MICELLAR MODELS OF BIOLOGICAL MEMBRANES.

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Biochim Biophys Acta; 648(1):107-112 1981

In 1976 we assayed pristane (2,6,10,14-tetramethylpentadecane) in a model interfacial system that has given excellent correlation with cocarcinogenic activity among n-alkanes, as tested in cycloalkane diluents. It was predicted that this branched-chain derivative of the diterpenes would have higher activity than n-C18H38, one of the most cocarcinogenic of the n-alkanes in such diluents. pristane was compared with n-C18H38 and two other n-alkanes for their promoting activities in cyclohexane for C3H male mice after a single application of 7,12-dimethylbenz[a]anthracene. The branched-chain alkane proved to be more active. Twenty percent n-tetracosane in cyclohexane was inactive, which correlated with its effects in this diluent in the physical assay system. The promoting activity of 75% n-octane in cyclohexane, predicted by the physical assay, was confirmed by tests on mice. The combined by-products of the synthesis of tetracosane, including C12 alkanes and alkenes, C19 and C20 alkylbenzenes, and C24 alkenes, proved to be a very active promoter. However, a mixture in cyclohexane of purified tetracosane with this composite of potential impurities was inactive. From the alkanes' behavior in physical systems involving various membrane phospholipids and steroids, it is hypothesized that the primary step in their biological activity is a chain-chain interaction with membrane lipids that alters the properties of liquid-crystalline phases at

aqueous interfaces. Resulting changes in the microfluidity of the lipid phase and the lateral mobility of critical hormone receptors and enzyme systems, such as the nucleotidyl cyclases, would perturb control systems that maintain the normal behavior of the initiated cell. Thus, its progression to a proliferating neoplasm may be favored. (Author abstract) (13 Refs)

26. MODIFICATION OF BENZO(A)PYRENE-INDUCED CELLULAR TRANSFORMATION OF C3H/10T1/2 CELLS BY DEXAMETHASONE AND PREGNENOLONE-16ALPHA-CARBONITRILE (MEETING ABSTRACT).

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In Vitro; 17(3):223 1981

Most chemical carcinogens exist in the environment in an unreactive form and require metabolic activation to exert their biological activity. Manipulation of the microsomal enzymes has been proposed as a mechanism for controlling carcinogenesis. In this study two compounds, dexamethasone (DEX) and pregnenolone-16alpha-carbonitrile (PCN), are potent inducers of microsomal enzymes in vivo. Since these enzymes are responsible for the metabolism of carcinogens, the effects of these compounds were studied to determine whether increased enzyme activity was correlated with cellular transformation. Both DEX and PCN were found to induce AHH activity in the C3H/10T1/2 cells by about 2 fold and both compounds increased the rate of metabolism of benzo(a)pyrene to water-soluble products. The steroids however had opposite effects on transformation. DEX inhibited cellular transformation by about 65% at 23 uM concentration. PCN, however, was found to increase the frequency of transformation by more than 100%. Therefore, enhanced AHH activity and metabolism does not necessarily lead to enhanced transformation since other pathways of metabolism, carcinogen detoxification, or repair processes may be involved. (no Refs)

27. EFFECTS OF CADMIUM IN VITRO ON BENZO(A)PYRENE METABOLISM BY RAT TESTICULAR AND HEPATIC MICROSOMES (MEETING ABSTRACT).

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Toxicologist; 1(1):121 1981

Cadmium is known to have toxic effects on the testes as well as to inhibit microsomal mixed function oxidase activity in a variety of tissues. Studies were carried out to compare the actions of cadmium in vitro on testicular and hepatic metabolism of benzo(a)pyrene (BP), a compound which requires metabolic activation for its mutagenic and carcinogenic effects. Testicular and hepatic microsomes were obtained from normal male rats and incubated with BP in the presence of saturating concentrations of NADPH and varying (2 x 10(-4) M -5 x 10(-6) M) concentrations of cadmium. In liver microsomes, cadmium produced a dose-dependent decrease in the production of fluorescent metabolites (phenols). By contrast, in testicular microsomes, the lower concentrations of cadmium (2.5 and 5 x 10(-5) M) enhanced the formation of phenols whereas higher levels (greater than 1 x 10(-4) M) decreased the production of fluorescent metabolites. To determine if the changes in testicular production of phenolic metabolites might be related to alterations in competing metabolic pathways, the effects of cadmium on the activity of epoxide hydrase, an enzyme required for the production of dihydrodiol metabolites, were investigated. Cadmium produced a dose-dependent inhibition of epoxide hydrase activity in both testicular and hepatic microsomes. The effects in testes were greater than those in liver. Preliminary analysis of BP metabolites by high performance liquid chromatography further indicates that cadmium affects the production of both phenols and dihydrodiols by testicular and hepatic microsomes. The results demonstrate that cadmium alters the routes of metabolism of BP in the testes and may therefore, influence its toxicity. (no Refs)

28. COMPARISON OF HEPATIC CARCINOGEN INITIATION-PROMOTION SYSTEM (MEETING ABSTRACT).

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Toxicologist; 1(1):154 1981

A number of model systems have been designed to study the initiating and promoting phases of neoplastic development in rat liver. The purpose of these experiments was to determine if the promoting protocols alone altered liver biochemistry. Four protocols, which use the same initiator, diethylnitrosamine (DEN), but different promotional regimens, were investigated. The biochemical parameters evaluated were hepatic microsomal benzphetamine-N-demethylase (BPND), epoxide hydratase (EH), cytosolic DT-diaphorase, serum glutamic pyruvic transaminase (GPT) and serum gamma glutamyl transpeptidase (GGT) activities. The effect of initiation in these protocols was also evaluated to ascertain if DEN caused changes in liver biochemistry and if these changes were related to preneoplastic lesions. All 4 promoting regimes depressed BPND (20-50% of control) and all except one increased EH and DTD (3-fold). SGGT was elevated by all protocols (10x) but SGPT was only slightly changed. The combination of DEN initiation with promotion increased hepatic GGT positive foci (identified histochemically) but did not alter the biochemical parameters studied. We conclude that measurement of these enzymes is of no value for predicting neoplastic change. However, the data show that liver biochemistry, especially with respect to drug metabolism, is extensively altered by the promotional regimes. Consequently, study of promoter-induced changes in drug metabolizing enzymes may lead to a better understanding of biochemical events during promotion in hepatocarcinogenesis. (4 Refs)

29. THE EFFECT OF PROMOTERS ON BLADDER CANCER INCIDENCE IN EXPERIMENTAL ANIMAL MODELS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Multistage models of carcinogenesis have been proposed to account for the observed patterns of tumor development in the skin, liver, lung, bladder and other organs. Such models involve initiation of neoplastic change in a few cells by a threshold dose of carcinogen, followed by conversion of these latent tumor cells into an autonomous cancer by further doses of the same and/or other carcinogens, and/or non-carcinogenic promoting agents. In the rat urinary bladder neoplastic change can be initiated by a few wk treatment with low doses of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) or N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) or by a single, low dose, intravesicular instillation of N-methyl-N-nitrosourea (MNU). Very few of the animals treated in such a way will develop

bladder cancer in their natural life span unless, in addition, they are exposed subsequently to some further regime which will promote tumor growth from the initiated tumor cells. Many different factors will promote tumor growth in the initiated rat bladder including further low doses of complete bladder carcinogens, some dietary factors such as metabolites of tryptophan or deficiency of vitamin A, the food additives saccharin and cyclamate, and some alkylating agents such as cyclophosphamide and methylmethanesulphonate. Although promoters do not necessarily have all the attributes of complete carcinogens, and may not be mutagenic, by accelerating the process of tumor development and thus lowering the age-related cancer incidence in any particular population they may be of prime importance in regulating overall cancer statistics. (no Refs)

30. PROTECTIVE EFFECT OF ETHANOL ON THE DEVELOPMENT OF PANCREATIC CANCER (MEETING ABSTRACT).

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No affiliation given
Newsletter Natl Pancreas Cancer Project; VI(2):61 1981

We examined the effects of chronic ethanol ingestion on pancreatic function and the appearance of pancreatic neoplasms in hamsters. Three groups of animals were fed standard laboratory chow and water ad lib. Group 1 received no other treatment. Group 2 received a single injection of N-nitrosobis(2-oxopropyl)amine (BOP) (20 mg/kg sc), a dose known to produce pancreatic carcinomas within 28 wk. Group 3 had ethanol added to the drinking water (25% wt/vol) for the duration of the study, and received the same dose of BOP 2 wk after starting the ethanol treatment. After 24 wk, pancreatic juice was collected following secretin and cholecystokinin stimulation, and the pancreases were examined histologically by one of us who had no knowledge of the treatment regimen. The presence of ductal proliferation (Proliferative Index, PI) and neoplastic lesions (adenoma, carcinoma in situ, carcinoma) was recorded. The blood ethanol concentration was 130 +/-8 mg% in Group 3 animals. Chronic ethanol ingestion was associated with significantly less preneoplastic ductal proliferation and fewer neoplastic pancreatic lesions. The explanation for this observation is uncertain, but it may be related to ethanol's known ability to alter the metabolism of pancreatic secretory cells. Thus the carcinogen may have been metabolized differently in these animals. (no Refs)

31. EFFECT OF INHIBITORS OF TUMORIGENESIS ON THE FORMATION OF O6-METHYLGUANINE IN THE COLON OF 1,2-DIMETHYLHYDRAZINE-TREATED RATS.

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Cancer Res; 41(12):4938-4941 1981

The level of O6-methylguanine (O6MeGua) in the colonic DNA of rats treated with 1,2-dimethylhydrazine was determined. The effect of various tumorigenesis inhibitors on the formation of this modified base was also studied. Rats were given a single sc injection of 1,2-[14C]dimethylhydrazine. Six hours later, they were killed, and colonic DNA was extracted and analyzed by high-pressure liquid chromatography. The inhibitors tested were disulfiram (DSF), pyrazole, sodium selenite, butylated hydroxyanisole, butylated hydroxytoluene, potassium ascorbate, and 13-cis-retinoic acid. The level of O6MeGua in control rats was 29.9 [(O6MeGua x 10(6)/guanine)]. When rats were fed 0.25% (w/w) DSF, this value was reduced to 10.2, and at 0.5% DSF there was not detectable O6MeGua formed. Injection of pyrazole (40 mg/kg ip) 2 hr prior to 1,2-dimethylhydrazine treatment reduced the O6MeGua level to 2.4. All the other tumorigenesis inhibitors had no effect on either O6MeGua levels or the cpm/mg DNA in treated rats. With O6MeGua as a measure of the extent of initiation, these results confirm that DSF and pyrazole inhibit the initiation phase of carcinogenesis. This is to be expected as both have been shown to block the metabolism of azoxymethane, which is a crucial metabolite in the activation of 1,2-dimethylhydrazine. The other substances, all known tumorigenesis inhibitors, may act on the promotional phase of carcinogenesis and are worthy of further study for their role in cancer prevention. (Author abstract) (22 Refs)

32. QUANTITATION OF A MUTAGENIC METABOLITE PRODUCED FROM 1,2-DIMETHYLHYDRAZINE DURING LIPID INFLUENCED COLON CANCER DEVELOPMENT BY A BACILLUS SUBTILIS ASSAY.

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Diss Abstr Int [B]; 42(4):1330-B 1981

The positive correlation between intake dietary fat and cancer of the colon is well documented. Studies were conducted using an experimental colon carcinogenesis model to determine the role of dietary fat in the metabolism of the colon carcinogen, 1,2-dimethylhydrazine (DMH). Bacillus subtilis TKJ6321 was used to quantify fecal mutagen and postmitochondrial enzyme in the liver and the colon mucosa of rats fed diets variable in lipid content and treated ip with DMH. Corn oil or coconut oil were used as the source of lipid for the diets. During a 32 wk schedule rats were sacrificed and autopsied for evidence of adenocarcinoma of the colon. Fecal samples were extracted and assayed for mutagenic activity by B subtilis TKJ6321 as the microbial detector of mutagenicity. Rats fed corn oil in the diet and treated with DMH produced a significantly higher number of adenocarcinomas of the colon. When the lipid content of the diet was raised to 10% (wt/wt) corn oil markedly stimulated enzyme induction in animals receiving DMH treatment. This induction was especially pronounced in the mutagen-producing enzyme activity of the colonic mucosa. Treatment of rats with DMH induces enzyme in the liver and colon relevant for the conversion of this compound to a mutagenic species. The extent of enzyme activity is influenced by the type of lipid supplementing the diet as is subsequent colon tumor development. (no Refs)

33. BUTYLATED HYDROXYTOLUENE PRETREATMENT REDUCES CYTOTOXICITY AND COVALENT BINDING OF AFLATOXIN B1 IN PRIMARY HEPATOCYTE CULTURES (MEETING ABSTRACT).

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Toxicologist; 1(1):108 1981

Primary cultures of adult rat hepatocytes were used to characterize the effect of butylated hydroxytoluene (BHT) pretreatment on the cytotoxicity and metabolism of a cytotoxic dose of aflatoxin B1 (AFB1). Male Sprague-Dawley rats were divided into two groups of four each, and fed either a control diet or one containing 0.5% BHT. After ten days, hepatocytes were prepared and cultured in chemically-defined, hormone-supplemented medium. After 20-22 hr in culture, 0.12-0.15 ug of [14C] AFB1 were added to dishes containing 2.5 x 10(6) cells. Medium was removed from sets of three cultures at 1/2, 1, 2,

4, 6, 10, and 24 hr thereafter, and extracted with chloroform. Cells were precipitated with 5% TCA and washed exhaustively with organic solvents. After 10 hr, control cells converted 59% of the AFB1 to aqueous metabolites, while 15% was bound covalently. During the same intervals, cells from BHT-fed rats produced 69% aqueous metabolites, and only 6% was bound covalently. AFB1-induced cytotoxicity was much greater in cells from control rats, as evidenced by release of lactate dehydrogenase (LDH) into the medium. Thirty-one hr after addition of AFB1, LDH levels in media from control cells av 1036+/-169 units/ml, while media from BHT-pretreated cells contained only 350+/-45 units/ml. BHT reduces cytotoxicity by apparently increasing the output of relatively nontoxic, water-soluble metabolites and decreasing the output of activated metabolites which covalently bind to macromolecules. Based on results from this in vitro model, we predict the BHT will also protect against AFB1-induced acute toxicity and carcinogenicity in vivo. (no Refs)

34. METABOLISM OF CYCLOPROPENOID FATTY ACIDS AND AFLATOXIN B1 IN ISOLATED HEPATOCYTES OF RAINBOW TROUT (SALMO GAIRDNERI) (MEETING ABSTRACT).

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Toxicologist; 1(1):34 1981

Rainbow trout are the most sensitive animal to Aflatoxin B1 (AFB) hepatocarcinogenicity. AFB1 is a potent carcinogenic mycotoxin occurring in contaminated peanuts, corn, and other grains. Trout feeding studies have also demonstrated the great synergistic hepatocarcinogenicity between AFB1 and cyclopropenoid fatty acids (CPFA). CPFA occur naturally in cotton-seed, kapok, and other food oils. Reason for this synergism has been the subject of much research. Hepatocytes were isolated in high viability (90% lactic dehydrogenase retained) from rainbow trout liver in situ by a two-step collagenase perfusion. Cells were incubated with CPFA and AFB1 and various metabolic parameters assessed. CPFA caused a dose-dependent fall in cellular glutathione (GSH) level, and a concomitant rise in lipid peroxidation occurred even in the absence of added ADP-Fe. The drop in GSH content was slower with CPFA than with diethyl maleate (DEM). Great excesses of either CPFA or DEM were required to significantly decrease cellular GSH. Binding of 3H-AFB1 to DNA was also investigated. AFB1 was rapidly bound to DNA in isolated hepatocytes. A dose of AFB1 added to cells after 0,1,2,3 or 4 hr preincubation resulted in the same level of DNA binding. Benzo(a)pyrene monooxygenase activity also remained constant for 4 hr. Cytotoxicity of AFB1 and the effect of CPFA on AFB1-DNA binding will be presented. (no Refs)

35. THE EFFECT OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF THE HEPATOCARCINOGEN 2-ACETYLAMINOFLUORENE IN THE RAT.

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Diss Abstr Int [B]; 42(4):1412-B 1981

Hepatic enzymes, presumably involved in the metabolism of the hepatocarcinogen 2-acetylaminofluorene (AAF), were examined in rats fed a Torula yeast-based selenium-deficient diet or the same diet supplemented with 0.5 ppm selenium (as sodium selenite). Selenium-deficient rats exhibited almost total absence of hepatic selenium-dependent glutathione peroxidase activity three wk after initiation of test diet feeding. Dietary selenium had no significant effect on hepatic soluble sulfotransferase activity in vitro as measured with the substrates, N-hydroxy-AAF and phenol. Hepatic lipid peroxidation (HLP) was not altered by AAF-challenge in rats fed either diet. In agreement with previous reports, dietary selenium protected against increased HLP produced by administration of carbon tetrachloride. Selenium-supplemented rats exhibited (a) no significant change in the production of 7-,5-, and N-hydroxy-AAF metabolites and (b) significantly increased production of 3-hydroxy-AAF metabolite as compared to selenium-deficient rats. Dietary selenium had no significant effect on total metabolites excreted or on the major phenolic metabolites excreted into the free-glucosiduronic acid-conjugated, or sulfuric acid-conjugated fractions. However, selenium-deficient rats excreted two and three x more N-hydroxy-AAF into the free-, and glucosiduronic acid-conjugated fractions, respectively. These findings tend to support the hypothesis that dietary selenium alters the in vivo metabolism of AAF in a manner that selectively decreases N-hydroxy-AAF excretion, and possibly its production. Thus dietary selenium's protective effect against AAF-induced hepatocarcinogenesis may be partially explained by the ability of selenium to decrease the amount of N-hydroxy-AAF available for further activation. (no Refs)

36. SULFATE-DEPENDENT METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY PRIMARY CULTURES OF ADULT RAT HEPATOCYTES (MEETING ABSTRACT).

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Toxicologist; 1(1):35 1981

The role of sulfate in the metabolic activation of the model aromatic amine hepatocarcinogen 2-acetylaminofluorene (2AAF) was determined using primary hepatocyte cultures as a cellular model of the liver. Adult male rat hepatocytes were isolated by collagenase perfusion of the liver and maintained in collagen-coated dishes with hormone-supplemented, chemically defined media. Cytochrome P-450 levels were fully maintained in the cultures for 48 hr. After 28 hr, the cultures were incubated with 67-137 ng of [14C]2AAF. Polar metabolites were isolated by chloroform-water partitioning, and bound carcinogen residues were measured as non-extractable radioactivity incorporated into hepatocellular trichloroacetic-acid-insoluble material. In an experiment using sulfate-free medium, sulfate supplementation doubled the level of bound residues at 2 and 3 1/2 hr but had no effect at 21 hr. Culture media containing 0, 0.1, 0.5 and 1.0 mM sulfate respectively produced 0.8, 1.4, 3.6 and 4.8% bound residues in a 3 hr incubation. Sulfate supplementation did not effect the overall rate of 2AAF metabolism. Phenol, at 1 uM in sulfate-free media, doubled the level of bound residues. Galactosamine, at 2mM, reduced by half the level of bound residues in cultures incubated with 2AAF and 1mM sulfate. These findings support the importance of sulfoconjugation in the metabolic activation of 2AAF. (no Refs)

37. MEMBRANE ALTERATIONS IN FUSING AND PHORBOL ESTER-TREATED MYOGENIC CELLS.

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Diss Abstr Int [B]; 42(4):1431-B 1981

Cultured chick embryo myogenic cells differentiate and fuse to form multinucleated myotubes which become striated and

acquire the potential to undergo spontaneous contractions. The diterpene tumor promoter, phorbol-12-myristate 13-acetate (PMA) inhibits myoblast fusion. The most rapid effects of this lipophilic compound occur in plasma membrane-associated processes, such as ion transport and cyclic nucleotide generation. Changes in specific membrane proteins have also been reported to occur in PMA-treated myogenic cells. In addition to the reported alterations in the levels of membrane proteins of known function it was possible that PMA extensively altered the composition and metabolism of other plasma membrane proteins whose functions are unknown. This hypothesis was tested using radiolabeled leucine and mannosamine precursors and electrophoretic analysis of membrane proteins on polyacrylamide gels. By 8 hr incubation PMA altered plasma membrane protein and sialoglycoprotein composition. Stimulation of diacylglycerol levels (2-fold) and stimulation of the rate of label incorporated into phosphatidic acid (2-fold), phosphatidylinositol (3-fold) and phosphatidylcholine (2-fold) were observed within 15-30 min of treatment with PMA. The increase in each of these lipids was shown to arise by synthesis from pre-existing lipids rather than by de novo synthesis. Using a double-label turnover technique and fatty acid analysis, it was shown that phosphatidylcholine is the most probable precursor of the PMA-induced diacylglycerol fraction. Subcellular fractionation of the PMA-stimulated cells suggested that the diacylglycerol was generated in the plasma membrane. Possible models for the mechanisms of PMA-dependent alterations in lipid metabolism and myoblast fusion are discussed. (no Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

38. LARGE DIFFERENCES IN METABOLIC ACTIVATION AND INACTIVATION OF CHEMICALLY CLOSELY RELATED COMPOUNDS: EFFECTS OF PURE ENZYMES AND ENZYME INDUCTION ON THE MUTAGENICITY OF THE TWELVE MONOMETHYLATED BENZ[A]ANTHRACENES, 7,12-DIMETHYLBENZ[A]ANTHRACENE AND BENZ[A]ANTHRACENE IN THE AMES TEST

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Carcinogenesis; 2(9):813-821 1981

Benz[a]anthracene, 7,12-dimethylbenz[a]anthracene (DMBA), and 12 isomeric monomethylbenz[a]anthracenes were all activated by C3H mice liver preparations to mutagens in Salmonella typhimurium TA100. However, the modes and requirements of metabolic activation differed widely for the different compounds. Some compounds were readily activated by the postmitochondrial liver fraction (S-9 mix) from control mice, but others were activated only by S-9 mix from 3-methylcholanthrene- or phenobarbital-treated mice. All compounds were mutagenic when activated with S-9 mix from Aroclor 1254-treated animals. Purified microsomal epoxide hydrolase almost completely inhibited the mutagenicity of some compounds, but it potentiated that of others, particularly K-region methylbenz[a]anthracenes. Purified cytosolic dihydrodiol dehydrogenase decreased the mutagenicity of the strong carcinogens DMBA, 7-methylbenz[a]anthracene, and 12-methylbenz[a]anthracene by up to 41%. In contrast, the enzyme had relatively moderate effects on the other compounds. None of the activating systems gave a quantitative correlation between mutagenicity and carcinogenicity in whole animal tests. (67 Refs)

39. LUNG AND LIVER CELL-MEDIATED MUTAGENESIS SYSTEMS: SPECIFICITIES IN THE ACTIVATION OF CHEMICAL CARCINOGENS.

Langenbach R, Nesnow S, Tompa A, Gingell R, Kuszynski C
Carcinogenesis and Metabolism Branch (MD 68), Genetic Toxicology Div., Health Effects Res. Lab., US Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 2(9):851-858 1981

Carcinogens from three chemical classes were compared for mutagenicity in systems containing cocultivated adult Sprague Dawley rat hepatocytes or lung cells and Chinese hamster V79 cells. 7,12-dimethylbenz[a]anthracene (DMBA), 3-methylcholanthrene (MCA), and benzo[a]pyrene (BP) were mutagenic for V79 cells in the lung cell-mediated system. DMBA and MCA were less mutagenic in the liver system, and BP was negative in this system. Aflatoxin B1 was mutagenic in the liver cell system but was only weakly mutagenic in the lung cell system. Dimethylnitrosamine (DMN) was mutagenic only in the presence of liver cells. The metabolism of BP and DMN was investigated to gain insight into the causes of their organ specificity. For DMN, the lack of metabolic activation by rat lung cells apparently accounted for its lack of mutagenicity in the lung cell-mediated system. BP was metabolized by both systems, but quantita tive differences were observed in the metabolites detected. Lung cells produced primarily the 7,8-and 9,10-diols and little detectable 4,5-diol, whereas liver cells produced the 4,5-diol as the major metabolite. (38 Refs)

40. METABOLISM OF N-NITROSO-2,6-DIMETHYLMORPHOLINE (NNDM) BY THE VARIOUS COMPONENT CELLS OF HAMSTER PANCREAS (MEETING ABSTRACT).

Scarpelli DG, Rao MS, Kokkinakis D, Hollenberg P
Department of Pathology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611
Newsletter Natl Pancreas Cancer Project; VI(2):52 1981

Hamster pancreas contains the necessary enzymes for activation of NNDM and N-nitrosobis(2-oxopropylamine) (NBOP) to forms mutagenic for Salmonella typhimurium. We report here on the metabolism of [3H]NNDM by S-9 and microsomes of whole pancreas (WP), and highly purified fractions of acinar cells (AC), and S-9 of islet cells (IC) isolated from normal and tetrachlorodibenzoparadioxin (TCDD) treated pancreas. Metabolism by duct and ductal cells was established by incubation of pancreatic slices in medium containing NNDM in the presence of [3H] thymidine with and without hydroxyurea to assess DNA repair. Analysis of metabolites by high pressure liquid chromatography showed that S-9 of WP, AC and IC metabolize NNDM to the following sequences of compounds respectively in descending order of concentration: N-nitroso(2-hydroxypropyl-2-oxopropyl)amine (HPOP) greater than NBOP greater than nitrosobis(2-hydroxypropyl)amine (BHP); NBOP greater than HPOP greater than BHP; and NBOP greater than BHP greater than HPOP. Addition of NADPH did not significantly alter metabolism of WP, but for AC led to increased formation of BHP; pretreatment with TCDD increased total metabolism in all instances. Microsomes of WP and AC produced the sequence NBOP greater than BHP greater than HPOP. TCDD increased (78%) total metabolism over that of controls. NADPH led to increased metabolism with both control microsomes (228%) and those isolated from TCDD pre-

treated animals (212%). Metabolism by S-9 and microsomes isolated from WP, AC and IC were about 1/20 those isolated from liver. Unscheduled DNA synthesis (repair) in nuclei of duct epithelium suggests that these cells are also capable of metabolizing NNDM. (1 Ref)

41. MUTAGENICITY OF ALKYL GLYCIDYL ETHERS IN THREE SHORT-TERM ASSAYS.

Thompson ED, Coppinger WJ, Piper CE, McCarroll N, Oberly TJ, Robinson D
Miami Valley Lab., Procter and Gamble Co., P.O. Box 39175, Cincinnati, OH, 45247
Mutat Res; 90(3):213-231 1981

Effect of alkyl chain length on the mutagenic potential of glycidyl ethers was examined in three in vitro assays, the Salmonella/mammalian microsome assay, the L5178Y mouse lymphoma assay, and by unscheduled DNA synthesis induced in WI38 human diploid fibroblasts. Glycidol, ethyl glycidyl ether, butyl glycidyl ether, and hexyl glycidyl ether were positive in the Salmonella revertant assay with or without metabolic activation, although enhancement of the response was seen in the presence of S9. Octyl glycidyl ether, decyl glycidyl ether, and dodecyl glycidyl ether induced a weak mutagenic response only in the presence of S9. Tetradecyl glycidyl ether was negative in this assay. In the mouse lymphoma assay, glycidol and the ethyl, butyl, and hexyl glycidyl ethers gave positive responses with or without S9. Octyl, dodecyl, and tetradecyl glycidyl ethers were negative. In the unscheduled DNA synthesis assay, positive responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for glycidol and ethyl glycidyl ether in the presence of S9. Weak responses were obtained for butyl glycidyl ether with S9 and ethyl glycidyl without S9, but other compounds were negative in this assay. (18 Refs)

42. MUTAGENICITY AND CYTOTOXICITY OF HALOETHANES AS STUDIED IN THE CHO/HGPRT SYSTEM.

Tan EL, Hsie AW
Graduate Sch. Biomedical Sciences, Univ. Tennesee, Oak Ridge, TN
Mutat Res; 90(2):183-191 1981

Mutagenic and cytotoxic effects of ethylene dibromide (EDB), ethylene bromochloride (EBC), and ethylene dichloride (EDC) as quantified in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase mammallian cell gene mutation assay are reported. All haloethanes tested exhibited mutagenic activity in the presence or absence of S9, in the order EDB greater than EBC greater than EDC. When tested as direct-acting agents, EDM, EBC, and EDC reduced cell survival to 50% at approx 3, 6, and 50 mM, respectively. Cell survival decreased with further increases in haloethane concentration. Cell survival dropped exponentially over a treatment time of 24 hr, but the mutagenic activity attained a max at approx 5 hr. The haloethanes were 5-25x more toxic in the presence of S9 than in its absence. S9-induced toxic metabolites were also more mutagenic to the cells. Such increased toxicity is NADPH-dependent. (22 Refs)

43. MUTAGENIC ACTIVITY IN DIESEL EXHAUST PARTICULATES.

Nachtman JP, Xiao-bai X, Rappaport SM, Talcott RE, Wei ET
Standard Oil Co. California, Richmond, CA, 94802
Bull Environ Contam Toxicol; 27(4):463-466 1981

The mutagenicity of chloroform eluates of diesel exhaust particulate extracts was examined by Ames test with or without S-9 mix. Exhaust eluates produced S-9-independent mutagenic activity of approx 480 revertants/100 ug of extract/plate. The addition of live enzymes decreased mutagenic activity. After reduction of the exhaust extract with sodium borohydride, the S-9-independent activity was greatly diminished. Addition of S-9 to the reduced sample revealed the presence of S-9-dependent mutagenic activity. Results suggest the presence of nitroarene mutagens in diesel exhaust particulates. (12 Refs)

44. MUTAGENICITY OF COSMETICS INGREDIENTS LICENSED BY THE EUROPEAN COMMUNITIES.

Gocke E, King MT, Eckhardt K, Wild D
Zentrallabor fur Mutagenitatsprufung, Deutsche Forschungsgemeinschaft, Breisacher Str. 33, D-7800 Freiburg/Breisgau, W. Germany
Mutat Res; 90(2):91-109 1981

Cosmetic ingredients allowed by the guidelines of the Council of the European Communities (27 July 1976) were investigated for mutagenicity in the Salmonella/microsome assay (SAL-m), the Basc test on Drosophila (Basc), and the micronucleus test on mouse bone marrow (MN). Of the 31 chemicals tested, 15 were mutagenic in SAL-m. Five of these were also mutagenic in Basc and two in the MN test. Only one compound, pyrogallol, was active in all three test systems. None of the compounds positive in the two eukaryotic systems was inactive in the SAL-m assay, which underlines the sensitivity of the Ames test with regard to various mutagens. Of the compounds positive in the SAL-m test, seven would not have been recorded if only the generally used Vogel-Bonner medium had been used. Of these substances, two were mutagenic in one or the other of the two eukaryotic test systems. (62 Refs)

45. MUTAGENICITY IN SALMONELLA OF DYES USED BY DEFENCE PERSONNEL FOR THE DETECTION OF LIQUID CHEMICAL WARFARE AGENTS.

Nestmann ER, Kowbel DJ, Wheat JA
Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, K1A OL2, Canada
Carcinogenesis; 2(9):879-883 1981

Six indicator dyes capable of detecting chemical warfare agents in liquid form were tested for mutagenicity in the Salmonella typhimurium/rat microsome plate incorporation assay. Ethyl-bis(2,4-dinitrophenyl)acetate, Orasol Navy Blue 2RB (TD-4), and Eastman Fast Blue G-BLF induced dose-related increases in His+ reversion mutations in three or more of the S typhimurium tester strains (TA153, TA100, TA1537, TA1538, and TA98). Papers in which the dyes were impregnated were also mutagenic. Thiodiphenyl-4,4'-diazo-bis-salicylic acid was weakly mutagenic in the plate assay but strongly mutagenic in a fluctuation assay. Fluorescent Brilliant Yellow R and 2,5,2',5'-tetramethyltriphyenyl methane-4,4'-diazo-bis-beta-hydroxynaphthoic anilide were not mutagens. (16 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

46. FORMATION OF COVALENT DEOXYRIBONUCLEIC ACID BENZO(A)PYRENE 4,5-EPOXIDE ADDUCT IN MOUSE AND RAT SKIN.

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Cancer Lett; 14(2):125-129 1981

The formation of benzo(a)pyrene DNA adducts was determined 24 hr after topical administration of labeled compound to the backs of female Swiss mice and male Wistar rats. Adducts corresp onding to authentic 4,5-dihydro-4,5-epoxy benzo(a)pyrene standards and to a further metabolite of 9-hydroxybenzo(a)pyrene were identified via high pressure liquid chromatography. (17 Refs)

47. BENZO(A)PYRENE METBOLISM AND COVALENT BINDING OF BENZO(A)PYRENE METABOLITES TO DNA.

Shen AL
University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):880-B 1981

Benzo(a)pyrene metabolism and covalent binding of benzo(a)pyrene metabolites to DNA have been investigated in liver microsomes and hepatocytes prepared from 3-methylcholanthrene treated rats and in C3H/10T1/2/CL8 mouse embryo fibroblasts. In both hepatocytes and microsomal incubations, the major benzo(a)pyrene DNA adducts formed were adducts of anti- and syn- isomers of (-)-trans-7,8-dihydroxy-9,10-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (diol-epoxides) and of epoxide derivatives of benzo(a)pyrene-9-phenol (phenol-oxides). Diol-epoxide adducts predominated in hepatocytes while the reverse was found in microsomal incubations. C3H/10T1/2/CL8 fibroblasts metabolized benzo(a)pyrene to products which bound covalently to DNA. The major adducts were those arising from anti- and syn-benzo(a)pyrene diol-epoxides. (no Refs)

48. METABOLISM OF BENZO[A]PYRENE BY HUMAN MAMMARY EPITHELIAL CELLS: TOXICITY AND DNA ADDUCT FORMATION.

Stampfer MR, Bartholomew JC, Smith HS, Bartley JC
(c/o Bartley) Peralta Cancer Res. Inst., Peralta Hosp., 3023 Summit St., Oakland, CA, 94609
Proc Natl Acad Sci USA; 78(10):6251-6255 1981

Pure cultures of human breast epithelial cells and of fibroblastic cells in early passage provided the opportunity to ask whether either cell type had the capability for metabolizing chemical carcinogens and, if so, was the fate of the metabolic products compatible with chemical carcinogens being a factor in the initiation of breast cancer in women. For this purpose, cells were exposed to benzo[a]pyrene (BaP), and (i) the influence on growth potential and (ii) the extent, type, and persistence of adducts between the metabolites of BaP and DNA were measured. Compared with fibroblasts, inhibition of growth by epithelial cells was 50-100x more sensitive to BaP. Because of this differential sensitivity, epithelial cells were exposed to 4.0 uM BaP and fibroblasts were exposed to 4.0 uM BaP in the studies of DNA adduct formation. Separation by high-pressure liquid chromatography of adducts between (+-)-7,8-dihydroxy-9,10-expoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BaP diol epoxide) and nucleosides from purified DNA revealed that epithelial cells contained modified DNA within 6 hr after adding BaP. Adducts between the 7R anti stereoisomer of BaP diol epoxide and deoxyguanosine predominated at all times. syn BaP diol epoxide adducts with deoxyguanosine and what appeared to be BaP diol epoxide adducts with deoxycytidine were consistentl y present but at much lower frequency. All three types of BaP diol epoxide-DNA adducts persisted in epithelial cells for 72 hr in BaP-free medium. No adducts were detected in fibroblastic cultures until 96 hr after first exposure to BaP. At this time, the type and extent of BaP diol expoxide-DNA adduct formation was similar to that in epithelial cells exposed to one-tenth the dose of BaP. The type, extent, rate of formation, and persistence of the adducts in human breast epithelial cells was similar to that in cells transformable by exposure to BaP, an indication that they may be targets for chemically induced carcinogenesis. (Author abstract) (42 Refs)

49. ACTIVATION AND DETOXIFICATION OF BENZO(A)PYRENE BY HAMSTER AND RAT HEPATOCYTES (MEETING ABSTRACT).

Raineri R, Polley JA, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability of hepatocytes from Syrian golden hamsters and Sprague-Dawley rats to metabolize and covalently bind [3H]-benzo(a)pyrene (BP) was examined. Following 3 hr incubation with 4.4 uM BP, hamster hepatocytes metabolized 95% of the BP; rat hepatocytes only 41%. There were 5 x more water-soluble metabolites in the medium from hamster than from rat hepatocytes. The levels of organic solvent-soluble metabolites (OSM) were similar. While beta-glucuronidase treatment of hamster hepatocyte medium increased the OSM, no such increase was seen after treatment of rat hepatocyte medium. The results were similar after treatment with arylsulfatase. When hepatocytes from Aroclor 1254 (AC)-treated animals were compared, increases in OSM after enzymatic deconjugation occurred only with hamster preparations. A 5-fold increase in levels of binding of BP to hamster hepatocyte RNA, and a 17-fold increase to rat RNA, occurred when hepatocytes from AC-treated animals were used. Increased levels of binding to rat hepatocyte DNA and protein were also seen. Although BP is not considered a liver carcinogen, we found high rates of conjugation and binding in liver cells. Initial metabolism may therefore occur in the liver followed by transport of conjugated metabolites and subsequent activation at the site of tumor induction. (no Refs)

50. THE EFFECT OF AN INDIVIDUAL'S BLOOD PRESSURE ON THE PERCENTAGE OF TOTAL 7,12-DIMETHYLBENZ[A]ANTHRACENE METABOLITES THAT BIND COVALENTLY TO DNA IN CULTURED RESTING LYMPHOCYTES.

Pero RW, Bryngelsson C, Ostlund C, Bryngelsson T, Norden A
Unit Community Care Sciences, S-240 10 Dalby, Sweden
Chem Biol Interact; 37(1):1-12 1981

A method for the quantitative analysis of the percent metabolism that results in covalent binding of 7,12-dimethylbenz[a]anthracene (DMBA) to DNA in viable resting human lymphocytes is described. The inter- and intra-experimental reproducibility as judged by the coefficient of variation and examined in the same individual over a 3-mo period was 31.4% and 13.9%, respectively. When the lymphocytes from 30 hypertensive individuals were exposed to 1 uM DMBA for 18 hr, the percent of total DMBA metabolites that bind DNA

covalently was correlated to the blood pressures of the patients at the time of sampling (r = 0.53, p less than 0.005). No influences on the data from the type or duration of hypertensive drug treatment could be statistically determined for this sample of hypertensive patients. It was concluded that high blood pressure is a strong determinant in predisposing lymphocytes to increased genetic risk from induced DNA damage and that this relationship is not statistically affected by hypertensive drug therapy. (Author abstract) (33 Refs)

51. THE DETERMINATION OF O(6)-METHYL- AND 7-METHYLGUANINE IN MOUSE LIVER DNA FROM DIMETHYLNITROSAMINE-TREATED MICE BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY WITH UV ABSORBANCE DETECTION.

Lawrence JF, Leduc R, Ryan JJ
Food Res. Div., Health Protection Branch, Tunney's Pasture, Ottawa K1A 0L2, Ontario, Canada
Anal Biochem; 116(2):433-438 1981

The methylated purines O6-methyl- and 7-methylguanine were isolated from mouse liver DNA hydrolysates by means of a column cleanup employing a Sep Pak C-18 reverse-phase cartridge. The purine bases were eluted from the cartridge with methanol, evaporated to dryness, and then dissolved in mobile phase for liquid chromatographic analysis by normal-phase chromatography. The system consisted of a LiChrosorb Si 60 column with a water-saturated mobile phase of 20% methanol in chloroform containing 0.001% H3PO4. The two methylated bases eluted before adenine or guanine. For extremely low-level (less than 300 pmol) quantitation, the peaks corresponding to O6-methyl- and 7-methylguanine were collected and then analyzed by reverse phase chromatography with LiChrosorb RP-18 column and mobile phase of 5% methanol in pH 7 phosphate buffer (for 7-methylguanine) or 9.5% methanol/buffer (for O6-methylguanine). Comparisons were made with fluorescence detection and with scintillation counting (in animal studies where [14C]dimethylnitrosamine was used). Minimum detectable levels at 254 nm were about 3 ng (3:1 signal to noise ratio) for each of the title compounds. As low as 10 pmol/mg of each could be detected in DNA hydrolysates. Recoveries of O6-methyl- and 7-methylguanine from DNA spiked at 750 pmol/mg were greater than 80%. (Author abstract) (20 Refs)

52. INDUCTION OF PANCREATIC DNA DAMAGE AND TUMORS IN RATS TREATED WITH N-NITROSO-BIS(2-OXOPROPYL)AMINE (MEETING ABSTRACT).

Longnecker DS, Zurlo J, Curphey TJ
Department of Pathology, Dartmouth Medical School, Hanover, NH, 03755
Newsletter Natl Pancreas Cancer Project; VI(2):35 1981

Differences in response of various species to carcinogens pose problems in regar d to extrapolation from animal experiments to man. In experimental pancreatic carcinogenesis, severai oxidized derivatives of dipropylnitrosamine have been effective pancreatic carcinogens in hamsters whereas they have failed to induce pancreatic cancers in rats. In studying this species difference we have used alkaline elution analysis to demonstrate DNA damage in pancreas of rats treated with N-nitrosobis(2-oxopropyl)amine (BOP) and N-nitroso-(2-hydroxypropyl-2-oxopropyl)amine (HPOP). Because these agents were effective in inducing DNA damage in pancreas, we treated young rats with a single dose of BOP (100 mg/kg) or HPOP (20 mg/kg) and autopsied them 4 mo later. Grossly visible nodules measuring up to 3 mm were present in pancreases of rats of both groups. Histologically the pancreases contained multiple foci and nodules of atypical acinar cells which were not seen in controls. Thus, BOP and HPOP induce both DNA damage and phenotypic changes in acinar cells in rats which are similar to those induced by the pancreatic carcinogens azaserine and Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine. Although rats appear to be less sensitive than hamsters to BOP, both species respond to comparable doses of HPOP. Our findings suggest that these compounds would induce pancreatic cancers in rats in studies of 1-2 yr duration if appropriate doses are given to young rats. (no Refs)

53. STUDIES ON NITROSAMINE METABOLISM. III. COMPARISON OF THE SUBCELLULAR DISTRIBUTION OF RADIOACTIVITY IN TISSUES OF RFM AND BALB/C MICE FOLLOWING ADMINISTRATION OF [14C]DIETHYLNITROSAMINE.

Daugherty JP, Clapp NK
Comprehensive Cancer Center, Univ. Alabama Sch. Medicine, Birmingham, AL, 35294
Res Commun Chem Pathol Pharmacol; 34(1):165-168 1981

The tissue distribution of radioactivity in male RFM and BALB/c mice was investigated following a single dose of [14C]-labeled diethylnitrosamine (DEN). The radiolabel was associated with all the subcellular fractions, and the majority of the radioactivity was located in the cytosol fraction. The majority of the radiolabel was usually eliminated from the fractions within 16-24 hr after [14C]DEN administration. (Author abstract) (4 Refs)

54. POTENCY OF AFLATOXIN B1 AND AFLATOXIN M1 IN CYTOTOXICITY AND DNA REPAIR ASSAYS (MEETING ABSTRACT).

Green CE, Rice DW, Hsieh DP, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):42 1981

Although the acute toxicity and carcinogenicity of aflatoxin B1 (AFB1) has been thoroughly documented, relatively little is known of the potency of aflatoxin M1 (AFM1), a hydroxylated metabolite of AFB1. Therefore, the cytotoxicity and genotoxicity of AFB1 and AFM1 were compared using in vitro system of primary cultures of rat hepatocytes. Hepatocytes were cultured for 20 hr (2.5 x 10(6) ce lls/dish) in hormone supplemented culture medium. The incubation was continued for an additional 24 hr with the test chemicals and 0.5 uCi/ml [3H] thymidine ([3H]TdR). Cytotoxicity was assessed by measuring lactate dehydrogenase released into the culture medium. Both AFB1 and AFM1 were potent cytotoxins. LDH levels were elevated significantly above controls for AFB1 at 0.1 ug/dish and for AFM1 at 0.6 ug/dish. However, LDH concentrations rose to the same max of approx 200% of controls for AFB1 and AFM1 at a dose of 1.2 ug/dish. Genotoxicity was assessed by measuring unscheduled DNA synthesis by two different methods, incorporation of [3H] TdR into trypsin-resistant acid-precipitable material and autoradiographic analysis. AFB1 and AFM1 were both positive and about equally potent in the DNA repair assay using either technique. In vivo experients indicate a higher level of DNA binding for AFb1 than AFM1. There are two plausible explanations for the DNA repair data; 1) AFB1 and AFM1 bind to DNA to approx the same extent in the hepatocyte culture system, 2) less AFM1 is covalently bound to DNA than AFB1 but AFM1 adducts are more efficiently repaired. (1 Ref)

55. ACTIVATION OF N-2-ACETYLAMINOFLUORENE BY TARGET AND NONTARGET SYRIAN GOLDEN HAMSTER CELLS (MEETING ABSTRACT).

Polley JA, Raineri R, Ernst MK, Andrews AW, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability to metabolize and activate N-2 acetylaminofluorene (AAF) of Syrian golden hamster kidney, bladder, small intestine, lung and liver cells was compared with that of hamster embryo fibroblasts. At varying times after isolation, cells were exposed to 5 ug [14C]-AAF for 3, 6 or 24 hr. The level of AAF remaining and the amount bound to cellular components were determined. Within 3 hr, hepatocytes and intestinal cells had metabolized 95% of the AAF. Within 6 hr lung cells had metabolized 50%, and kidney cells 20%. By contrast, fibroblasts and bladder cells had metabolized only 20-25% in 24 hr. The amount of material bound to cellular components was proportional to the amount of AAF metabolized. A second measure of activation was the ability of intact organ cells to metabolize AAF to a form mutagenic in Salmonella TA 1538. Revertant numbers were much increased above background with hepatocytes (240-fold), lung cells (11-fold), intestinal cells (5-fold) and kidney cells (2-fold). With bladder cells and fibroblasts, revertant numbers were not significantly higher. We have demonstrated that intact cells, whether or not from the target organ, can metabolize AAF at a high rate to forms which either bind to cellular components or are excreted. These forms are also mutagenic in Salmonella. (no Refs)

56. PROSTAGLANDIN SYNTHETASE CATALYZED DNA STRAND BREAKS BY AROMATIC AMINES (MEETING ABSTRACT).

Rahimtula A, Moldeus P, Nordenskjoeld M, Andersson B
Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Several aromatic amines are renal medullary toxins and bladder carcinogens. We have found that the aromatic amines 2-naphthylamine, 2-4-diaminotoluene, p-aminophenol and p-phenetidine at a concentration of 50uM cause a 2-3 fold increase in DNA strand breaks in cultured human fibroblasts in the presence of sheep vesicular gland microsomes and arachidonic acid. Indomethacin and butylated hydroxyanisole inhibited this reaction. Curiously, benzidine did not give rise to a significant increase in DNA strand breaks. Metabolism of these amines by prostaglandin synthetase was judged by their ability to complete with and inhibit another prostaglandin synthetase dependent reaction - the activation of paracetamol. An 0.1 mM concentration of these amines inhibited the glutathione conjugate formation of paracetamol by 60-90%. Covalent protein binding of [3H]paracetamol was similarly inhibited. At the concentration used, these amines did not significantly affect the cyclooxygenase activity as judged by prostaglandin E2 and prostaglandin F2alpha formation. (2 Refs)

57. PROSTAGLANDIN SYNTHETASE MEDIATED ACTIVATION OF P-DIMETHYLAMINOAZOBENZENE (BUTTER YELLOW) (MEETING ABSTRACT).

Vasdev S, Tsuruta Y, O'Brien P
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The oral administration of dimethylaminoazobenzene (DAB) induces rodent liver tumors, mouse lung tumors and dog bladder tumors. It is believed that the activation by the liver of DAB involves liver microsomal mixed function catalyzed sequential N demethylation and N hydroxylation reactions. A cytosolic sulfotransferase then catalyzed the conjugation of the N-OH derivative with sulfate to form an electrophilic species which can bind to nucleic acids and protein. This electrophile is considered to be the ultimate carcinogenic metabolite. An alternative metabolic activation should now be considered. It has been found that prostaglandin synthetase can catalyze the binding of C14 DAB to microsomal protein. Extensive N demethylation occurred and C14 4-methylaminoazobenzene was much more effective at binding to the protein than DAB. Arachidonate was also more effective than NADPH with mouse lung and dog bladder microsomes. Cumene hydroperoxide was also much more effective than NADPH with rat liver microsomes. However, cytochrome P 450 was the catalyst for the latter hydroperoxide reaction as in this case extensive 4'hydroxylation also occurred. (no Refs)

58. METABOLISM AND MACROMOLECULAR BINDING OF THE CARCINOGEN MICHLER'S KETONE IN RATS.

Struck RF, Shih TW, Johnston TP, Kirk MC, Hill DL
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Xenobiotica; 11(8):569-577 1981

Studies on the metabolism of 14C-Michler's ketone (4,4'-bis-(dimethylamino)[carbonyl-14C]benzophenone) in rats have revealed that this carcinogen is subject to demethylation, ring-hydroxylation and N-acetylation after adjacent methyl groups have been removed. As identified by mass spectral analysis, microsomal metabolites are the mono-, di-, tri- and tetra-demethylated derivatives. The major metabolites appearing in the bile are the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound; minor metabolites, tentatively identified, are the ring-hydroxylated derivatives of di- and tri-demethylated Michler's ketone and of N-acetylated tri- and tetra-demethylated Michler's ketone. The major urinary metabolite is tentatively identified as a ring-hydroxylated derivative of N-acetylated, di-demethylated Michler's ketone; a minor urinary metabolite lacks the hydroxyl group. Injection of 14C-Michler's ketone into rats resulted in the irreversible binding of radioactivity to liver proteins. When the rats were pretreated with phenobarbital, this binding was increased and extended to proteins of some other tissues and to DNA and RNA of liver and DNA of kidney. (Author abstract) (13 Refs)

59. PROSTAGLANDIN HYDROPEROXIDASE-MEDIATED 2-AMINO-4-(5-NITRO-2-FURYL)[14C]THIAZOLE METABOLISM AND NUCLEIC ACID BINDING.

Mattammal MB, Zenser TV, Davis BB
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Cancer Res; 41(12):4961-4966 1981

Prostaglandin hydroperoxide-mediated metabolism and binding of 2-amino-4-(5-nitro-2-furyl)[14C]thiazole ([14C]ANFT) metabolite to nucleic acids and proteins were investigated with rabbit bladder transitional epithelial and solubilized ram seminal vesicle microsomes. Metabolism was assessed by spectrophotometric and radiochemical techniques. Substrate and inhibitor studies are consistent with both metabolism and binding of [14C]ANFT occurring by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase. The ratio of the rates of [14C]ANFT product formation is approx 3:7:10 (organic soluble:non-trichloroacetic acid precipitable: trichloroacetic acid precipitable) over a wide range of arachidonic acid concentrations. Approx 2 and 1% of the total [14C]ANFT metabolized binds to transfer RNA and DNA, respectively. The metabolite isolated from the organic phase had a chromatographic profile and UV spectra different from authentic ANFT. If transfer RNA or DNA is added at the end of a 5-min incubation , no binding to nucleic acids was observed. The demonstration of prostaglandin hydroperoxidase-mediated covalent binding to nucleic acids is consistent with the involvement of this enzyme in 5-nitrofuran-induced bladder carcinogenesis. (Author abstract) (44 Refs)

60. IN VITRO METABOLISM OF ACRYLONITRILE TO 2-CYANOETHYLENE OXIDE, REACTION WITH GLUTATHIONE, AND IRREVERSIBLE BINDING TO PROTEINS AND NUCLEIC ACIDS.

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Cancer Res; 41(12):4925-4933 1981

The metabolism of the suspected carcinogen acrylonitrile was studied using subcellular fractions isolated from rats and humans. Irreversible binding of radioactive label from [1-14C]- or [2,3-14C]acrylonitrile to protein and DNA was enhanced by reduced nicotinamide adenine dinucleotide phosphate in the presence of rat liver microsomes or a reconstituted cytochrome P-450 system. During the reduced nicotinamide adenine dinucleotide phosphate-dependent reaction, HCN was produced, and the heme of cytochrome P-450 was destroyed. Rat brain microsomes did not produce detectable levels of metabolites. Conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems was not found. With rats, metabolism was induced by pretreatment of animals with either phenobarbital or 5,6-benzoflavone. Labeled 2-cyanoethylene oxide was found to bind irreversibly to calf thymus DNA and microsomal protein. The extent of binding was greater in the case of 2,3-14C-labeled than 1-14C-labeled material. The relative first-order rate of acrylonitrile binding to calf thymus DNA in rat liver microsomal systems was one to two orders of magnitude less than that for 1,1,2-trichloroethylene and three orders of magnitude less than that for vinyl chloride or vinyl bromide. Rat liver microsomes or a reconstituted cytochrome P-450 system catalyzed the mixed-function oxidation of acrylonitrile to 2-cyanoethylene oxide. 2-Cyanoethylene oxide has a half-life of about 2 hr in neutral buffer at 37 C. This epoxide was found to serve as a substrate for microsomal epoxide hydrolase. HCN was released during hydrolysis of 2-cyanoethylene oxide or reaction of the epoxide with reduced glutathione; however, HCN release in either case was not stoichiometric with epoxide disappearance. 2-Cyanoethylene oxide reacted less rapidly with reduced glutathione than did acrylonitrile. Rat liver cytosol preparations contained glutathione S-transferase activity towards acrylonitrile and greater activity with 2-cyanoethylene oxide as a substrate. Cytosol preparations from rat brain and human liver had no detectable glutathione S-transferase activity towards acrylonitrile but did exhibit some activity towards 2-cyanoethylene oxide. These studies establish the basic pathways involved in the metabolism of acrylonitrile and should provide a basis for examination of the relevance of these individual steps and their roles in bioactivation and detoxication under more physiological situations. (Author abstract) (40 Refs)

61. THE MOLECULAR BASIS FOR COMPLEXATION OF ADRIAMYCIN WITH FLAVIN MONONUCLEOTIDE AND FLAVIN ADENINE DINUCLEOTIDE.

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Arch Biochem Biophys; 212(1):20-36 1981

A molecular level investigation of the interaction of anthracycline (ATC) antibiotics with flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) was conducted in view of the potential significance of such reactions in cardiotoxicity and drug metabolism and the ability of NADPH-cytochrome P-450 reductase to most effectively catalyze the reduction of adriamycin (ADM) with electron transfer via the FMN (or FAD) prosthetic group. The nature, strength, and specificity of ADM complex formation with FMN or FAD was studied. Results indicated that ADM can produce saturable, temperature- and concentration-dependent shifts of certain proton resonances of FMN and FAD to high field. The structures of FMN, FAD, and ADM in soln, as well as the mechanism of self-association, are requisite to the development of a molecular model for the ADM-FMN or the ADM-FAD complex. The most likely configuration assumed for the FMN-ADM complexation positions the planar rings of ADM over the aryl ring of FMN such that maximal ring current effect is experienced by the H-9 proton of FMN. A similar orientation is expected for the FAD-ADM complex. The formation of bimolecular complexes between the flavins and ADM, such that the ADM quinone moiety is positioned above the aromatic rings of isoalloxazine, appears to be consistent with the activity of flavoprotein reductases toward ADM. Cytochrome P-450 reductase exhibits a 30-fold greater activity towards ATC reductive glycosidic cleavage than the next most active reductase enzyme, xanthine oxidase, which contains only FAD as its prosthetic group. It was a suggested that a correlation may exist between the formation of molecular level complexes involving ATC antibiotics and FMN or FAD, the metabolic generation of ATC-free radicals, and reactive oxygen species and ATC-induced cardiotoxicity. (43 Refs)

62. IN VITRO AND IN VIVO COVALENT BINDING OF THE KIDNEY TOXICANT AND CARCINOGEN TRIS(2,3-DIBROMOPROPYL)-PHOSPHATE.

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Toxicology; 21(4):291-304 1981

Incubation of 3H-tris(2,3-dibromopropyl)-phosphate (TRIS-BP) with rat liver microsomes led to its activation to products

which bound covalently to microsomal protein. The reaction was NADPH -dependent, and boiled microsomes yielded no binding. The reaction could be inhibited by nitrogen; carbon monoxide, which inhibits cytochrome P-450-mediated reactions, also reduced binding rates significantly. SKF 525-A and metyrapone, a selective inhibitor of phenobarbital-inducible cytochrome P-450, inhibited TRIS-BP activation. Alpha-napthoflavone, a selective inhibitor of cytochrome P-448, had little effect. Addition of glutathione and N-acetylcysteine markedly inhibited binding, but ascorbic acid did not. Paraoxon, an esterase inhibitor, and 1,1,1-trichloropropene-2,3-epoxide and cyclohexene oxide also were without effect. Rat kidney microsomes were capable of activating TRIS-BP to 8% of the level achieved by rat liver microsomes. Administration of TRIS-BP to rats resulted in considerable binding to kidney proteins, with lesser amounts detected in liver and very little in muscle proteins. Liver microsomes activated TRIS-BP to bind to DNA in vitro, but kidney microsomes did not. (31 Refs)

63. SPECIES DIFFERENCES IN MUTAGENICITY, COVALENT PROTEIN BINDING AND NEPHROTOXICITY OF THE FLAME RETARDANT TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (MEETING ABSTRACT).

Soderlund E, Dybing E, Nelson SD
Department of Toxicology, National Institute of Public Health, Olso, Norway
Acta Pharmacol Toxicol; 49(Suppl1):48 1981

Tris(2,3-dibromopropyl)phosphate (Tris-BP), the major flame retardant formerly used in US sleepwear, is a potent mutagen, a nephrocarcinogen and an acute nephrotoxin. Hepatic microsomes from rats, mice, hamsters, and guinea pigs are all able to activate Tris-BP to mutagenic products in the Salmonella microsome quantitative reversion assay, mice microsomes being the most and guinea pig microsomes the least active. Phenobarbital (PB)-pretreatment increases the mutagenic activity with all microsomal preparations, whereas 3-methylcholanthrene (MC)-pretreatment decreases Tris-BP mutagenicity in rats and mice and gives a moderate increase in hamsters and guinea pigs. Hepatic microsomes from all species tested have approx similar basal capabilities in converting Tris-BP to covalently protein bound products in vitro; PB-pretreatment increases binding rates in all preparations, MC-pretreatment increases Tris-BP covalent binding with hamster and guinea pig microsomes but not with microsomes from rat or mouse liver. Tris-BP binds covalently to liver protein in vivo in all species and to kidney protein in hamster, guinea pig and mouse to the same degree. In rat kidneys, on the other hand, seven fold higher protein binding levels are found compared to liver, correlating with the finding that kidney is the target organ in this species. None of the other species showed any Tris-BP-induced kidney damage. (no Refs)

64. THE MULTIPLE ROLES OF ESTROGEN IN ESTROGEN-DEPENDENT RENAL CLEAR-CELL CARCINOMA OF SYRIAN HAMSTER (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Estrogen (estradiol [E2] or diethylstilbestrol [DES]), when implanted subcutaneously into male Syrian hamster, elicits renal clear-cell carcinoma after approx 6-8 mo. Estrogen alone causes this effect, ie no cocarcinogen is required for tumor initiation or growth response. Studies conducted in our laboratories and elsewhere indicate that the elevated level of estrogen in the hamster results in a variety of different responses and biochemical effects which in a concerted fashion lead to the phenomenon called renal clear-cell carcinoma. DES and E2 induce peroxidase activity and microsomal P450 enzymes in a variety of tissues. In turn, peroxidase and microsomal P450 enzymes oxidize DES to a quinoid structure. DES quinone, a chemically unstable and reactive substance, may spontaneously rearrange to beta-dienestrol or, in the vicinity of cellular macromolecules, may covalently bind to DNA. DES-DNA adduct formation was studied in vitro under various conditions. H301 tumor cells, which are derived from the estrogen-dependent renal clear-cell carcinoma of Syrian hamster, remain estrogen-dependent in culture or in host animals. Upon removal of the hormone implant, tumors immediately shrink in size and disappear within 10 days. Estrogen concentration in tumor tissue is low (12-30% of estrogen uptake of liver), despite the presence of estrogen receptors in tumor tissue. (no Refs)

65. METABOLIC ACTIVATION OF DIETHYLSTILBESTROL BY PROSTGLANDIN SYNTHETASE AS A MECHANISM FOR ITS CARCINOGENICITY (MEETING ABSTRACT).

Bennett S, Marshall W, O'Brien PJ
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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The synthetic estrogen diethylstilbestrol (DES) induces kidney tumors in hamsters and genital tract tumors in rodents. Cervicovaginal alterations including carcinoma were also observed in the female offspring of DES treated women, as were certain teratogenic changes in the genital tract of their male progeny as a result of its transplacental toxicity. Metzler et al 1978 have suggested that peroxidases of estrogen target organs are responsible by catalyzing DES oxidation to intermediate that bind to nucleic acids and other cellular macromolecules. Our research shows that prostaglandin synthetase could also be a catalyst. Seminal vesicular microsomes and uterine microsomes readily catalyzed the binding of C14 diethylst ilbestrol to DNA and protein in the presence of arachidonate but not NADPH. Similar results were obtained with C14 estradiol and could explain the association of estrogens and cancer of tissues whose growth is effected by estrogen. DES also induces liver necrosis in vivo. Blackburn et al 1977 have shown that liver microsomes with NADPH catalyzes the binding of DES to DNA. We have also found that cumene hydroperoxide is much more effective than NADPH in catalyzing this binding. (no Refs)

66. THE INVOLVEMENT OF PROSTAGLANDIN INTERMEDIATES IN COVALENT BINDING TO NUCLEIC ACIDS AND IN AGEING PIGMENT FORMATION (MEETING ABSTRACT).

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Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Eling et al 1979 have shown that incubation of 1-C14 arachidonic acid with the microsomes of platelets, guinea pig lung, rabbit kidney and rat stomach fundus results in substantial binding to the protein. We also find that prostaglandin synthetase catalyzes the binding of arachidonate to exogenous DNA and RNA to form a fluorescent product. Prostaglandin could therefore play some role in carcinogenesis. The binding of prostaglandin intermediates to microsomal protein resulted in extensive crosslinking and polymerization of some proteins. This was prevented by glutathione or antioxidants and suggests that free radicals were involved. The formation of fluorescent products in the microsomes was attributed to conjugated schiff base product formation from the reaction between phospholipid amines and aldehyde. The spectra was similar to lipofuscin. In vivo lipofuscin pigment formation has been associated with aging, vitamin E deficiency, polyunsaturated fatty acid feeding and the ingestion of various environmental xenobiotics. The various tissues involved were lung, liver, heart, spleen, brain, kidney and testis. Incubation of the microsomes from these tissues with arachidonate resulted in protein polymerization and fluorescence formation. (no Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

67. METABOLIC ACTIVATION IN TYPE II ALVEOLAR LUNG CELLS OF THE RAT WITH EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

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In Vitro; 17(3):201 1981

L-2 cells clonally derived from adult rat lungs with characteristics of type II pneumonocytes exhibited elevated aryl hydroxylase (AHH) and epoxide hydratase (EH) activity following exposure to benzo(a)pyrene [B(a)P]. Max AHH activity was measured fluorometrically at 24 hr and increased linearly over this time period. Peak AHH activity was 10 x that of basal levels while peak EH activity w as about twice basal levels. Nuclear AHH activity was 10 percent that of the whole cells. Theophylline inhibited AHH activity and binding of tritium-labeled metabolites to nuclear macromolecules whereas the prostaglandin synthetase inhibitors indomethacin and sodium meclofenamate stimulated AHH activity and binding of labeled metabolities to nuclear macromolecules. Both the organic and water soluble metabolites extracted from the culture medium failed to produce mutagenesis in four strains of Salmonella typhymurium and in Chinese hamster V-79 cells. Unscheduled DNA synthesis was not observed in L-2 cells exposed to B(a)P. These results suggest that the enzyme activation and subsequent metabolism of benzo(a)pyrene in L-2 cells yields nonmutagenic and noncarcinogenic products and if representative may offer a partial explanation for the low incidence of type II cell involvement in human lung cancer. (1 Ref)

68. CHARACTERIZATION OF BENZOPYRENE HYDROXYLASE ENZYME ACTIVITY IN RAT PANCREAS (MEETING ABSTRACT).

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Medical Research Service, Veterans Administration Medical Center, Augusta, GA, 30912
Newsletter Natl Pancreas Cancer Project; VI(2):11 1981

The increasing incidence of pancreatic cancer, the growing environmental pollution problems, and our increased knowledge of interactions of various exogenous factors such as diet, sex, etc, heightens the need for information on etiology of pancreatic cancer. There are presently several models of carcinogen-induced cancer. Establishment of the capability of tissue to form active intermediates is necessary to establish a relationship between exposure to carcinogens and subsequent tumorigenic response. The present studies were undertaken to characterize the pancreatic metabolic system, specifically that which metabolizes the ubiquitous carcinogen, benzopyrene (BP). We determined the Km and Vmax of the BP hydroxylase enzyme reaction in male Sprague Dawley rats pretreated with 20 mg/kg 3-methylcholanthrene (3MC), 75 mg/kg phenobarbital (PB), or solvent as control. Type of cytochrome involved was examined by measuring the reaction in the presence of 7,8-benzoflavone (BF), an inhibitor of the cytochrome P-448-related enzyme activity. The data indicated that the enzyme activity was induced by pretreatment with PB but not with 3MC. These pretreatment protocols resulted in changes both in Km and Vmax. Studies with BF suggested that pancreatic tissue contained only one hemoprotein and point out species differences between the rat and guinea pig. These studies confirm the pancreatic capability to metabolize procarcinogens and to further degrade carcinogenic metabolites, and strengthens the role of carcinogen exposure in the etiology of pancreatic cancer. (no Refs)

69. THE INFLUENCE OF POLYCYCLIC AROMATIC HYDROCARBONS AS INDUCERS OF MONOOXYGENASES ON THE METABOLITE PROFILE OF BENZ(A)ANTHRACENE IN RAT LIVER MICROSOMES.

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Cancer Lett; 14(2):175-185 1981

Changes in metabolite profiles resulting from induction of monooxygenases by polycyclic aromatic hydrocarbons (PAH) in Wistar rats is reported. Benz(a)anthracene (BA) was used as substrate. Rat liver microsomes converted BA preferentially into 5,6-, 8,9-, and 10,11-trans-dihydrodiols. With control microsomes, approx 5x more 10,11-trans-dihydrodiol than 5,6-and 8,9-dihydrodiol was formed. All tested inducers increased the epoxidation at the 5,6-position and to a lesser extent at the 8,9-position. Oxidation at the 10,11-position, however, was decreased after almost all inducers. Treatment with more effective inducers resulted in an increased secondary metabolism, especially the formation of the bay-region dihydrodiol epoxide. While phenobarbital and the moderately-inducing PAH induced oxidation at the 5,6-and 8,9-positions, other compounds, especially the benzofluoranthenes, also induced oxidation at the 3,4-position. This reaction leads to formation of the ultimate

carcinogen of BA, 3,4-dihydroxy-1,2-epoxy-1,2,3,4 tetrahydrobenz(a)anthracene. (35 Refs)

70. ENZYME INDUCTION AND HEPATIC GLYCEROLIPID SYNTHESIS IN RATS TREATED WITH 3-METHYLCHOLANTHRENE.

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Can J Biochem; 59(9):793-798 1981

Fasting male rats fed 3-methylcholanthrene in a daily dose of 40 mg/kg body wt-1 gave evidence of hepatic microsomal enzyme induction after 3 days through significantly increased hepatic aryl hydrocarbon hydroxylase activity, cytochrome P448 content, and characteristic changes in microsomal proteins analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Concomitantly, activities of aminopyrine N-demethylase and microsomal gamma-glutamyltransferase, which are increased in phenobarbital-treated rats, significantly declined. In contrast to phenobarbital, which has been previously shown to increase hepatic triacylglycerol content and in vitro glycerolipid synthesis, 3-methylcholanthrene did not affect hepatic triacylglycerol content, but did inhibit glycerolipid synthesis by cell-free preparations of rat liver and significantly reduced serum triacylglycerol concentration. Thus, the two prototypical drugs inducing characteristically different changes in microsomal enzyme and hemoprotein response also seem to differ in their effect upon another important microsomal function, hepatic glycerolipid synthesis. (Author abstract) (31 Refs)

71. IMIDAZOLE DERIVATIVES AS INHIBITORS OF CYTOCHROME P-450-DEPENDENT OXIDATION AND ACTIVATORS OF EPOXIDE HYDROLASE IN HEPATIC MICROSOMES FROM A MARINE FISH.

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Biochem Pharmacol; 30(20):2876-2880 1981

Binding of 4(5)-phenylimidazole, benzimidazole, and naptho(2,3,4',5')-imidazole to cytochrome P-450 in sheepshead hepatic microsomes was examined; effects of these compounds on benzo[a]pyrene metabolism in control and induced microsomes are described. (39 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

72. PULMONARY METABOLISM OF PROSTAGLANDINS E2 AND F2ALPHA BY HAMSTERS TREATED WITH BENZO(A)PYRENE (MEETING ABSTRACT).

Huot J, Dufour M
Department of Pharmacologie, Universite Laval, Quebec City, Quebec, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Benzo(a)pyrene is a potent pulmonary carcinogen. We hypothesized that the chronic exposition of the lung to this toxic agent produces alteration of the prostaglandin metabolism. This was tested by studying the biotransformation of the prostaglandin E2 and prostaglandin F2 alpha by perfused ister lung. During 15 wk, one group of animals rec tratracheal administration of a suspension of benzo mg) adsorbed to charcoal in saline; a second grou charcoal saline suspension whereas only saline v tered to the third group. Prostaglandins and their were separated by thin-layer chromatography an by liquid scintillation. In all groups the prostaglan F2 alpha were respectively metabolized at 65% ar main metabolites were the 13-14 dihydro-15-keto the 13-14 dihydro-15-keto PGF2 alpha. The other were the 15-keto PGE2 the 15-keto PGF2 alpha. 15% of the PGE2 and 20 at 25% of the PGF2 found after a first passage through the lung. In ha ed for 15 wk, benzo(a)pyrene produced morphol ations of the lung structure and increased the lung er, our results suggest that the pulmonary metabo taglandins E2 and F2 alpha is not altered in these Refs)

73. INDUCTION OF ORNITHINE DECARBOXY CULTURED MAMMARY TUMOR CELLS (MEI ABSTRACT).

Cohen LA, Van der Snoek L
Naylor Dana Institute for Disease Prevention, Valhalla,
In Vitro; 17(3):242 1981

At present, little is known concerning the role p lyamines in mammary cancer. Since in vivo studie to interpret at the cellular level, we have develop in vitro system consisting of neoplastic epithelial from an N-nitrosomethylurea induced rat mamm cinoma. Ornithine decarboxylase (ODC), the rate in polyamine synthesis, was measured in these ce situ method of Patterson and Maxwell. To induc log-phase cells were grown in serum-depleted me netics of ODC induction was similar to that repo cell lines. Specific activity (sp act) at 0, 15 and 60 than 0.5, 3.25 and 6.30 nmoles carbon dioxide/mg spectively; between 1 and 2 hr little change in sp served. The specificity of the reaction was assesse of inhibitors of the reaction mixture for the 2 hr There was an absolute requirement for pyridox the reaction product, putrescine, inhibited ODC mic fashion, and the competitive inhibitor alpha-ine reduced enzyme activity by half. (1 Ref)

74. TUMOR PROMOTION AND PROSTAGLA (MEETING ABSTRACT).

van Rooijen LA, Bisschop A
Department of Carcinogenesis and Mutagenesis, Natio Public Health, Bilthoven, The Netherlands
International Conference on Prostaglandins and Can September 2, 1981, Washington, DC. Lombardi Ca pp., 1981.

The tumor promotors 12-O-tetradecanoylphor (TPA) and phenobarbital both appear us to induc of rat hepatic ornithine decarboxylase (ODC). Th dose dependent, with an optimum dose at 20 ug per kg body wt and at 100 mg phenobarbital pe The ODC activity has a maximal value at 4 hr tion of the tumor promotor. It further is prote synthesis dependent. Treatment with retinyl-ac prior to TPA results in a dose dependent inhibiti at 20 mg per kg body wt, of the induce ODC ac acetate at this dose fails to inhibit the phenob

activity. Analogical pretreatment with indomethacin shows an inhibition of the induced ODC activity, which raises the suggestion of the involvement of prostaglandins in the sequence of events from the application of the tumor promotor to the increase in activity of rat hepatic ornithine decarboxylase. Ip application of prostaglandins (PG E2 and PG F2alpha) both appear to inhibit ODC activity. These two observations possibly suggest a difference in mode of action between intra- and extracellular prostaglandins. (no Refs)

75. EFFECTS OF VARIOUS CHEMICALS INCLUDING BILE ACIDS AND CHEMICAL CARCINOGENS ON THE INHIBITION OF METABOLIC COOPERATION.

Noda K, Umeda M, Ono T
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Gan; 72(5):772-776 1981

The effects of various chemicals, such as bile acids, a lectin, polyamines, and chemical carcinogens, on metabolic cooperation in the hypoxanthine-guanine phosphoribosyl transferase sys tem were surveyed. Among bile acids, lithocholic acid, chenodeoxycholic acid and ursodeoxycholic acid inhibited metabolic cooperation. However, cholic acid, deoxycholic acid and dehydrocholic acid did not. There was a structure-activity relationship among these compounds for the inhibition of metabolic cooperation. The metabolic cooperation was not inhibited by such chemicals as phytohemagglutinin, three polyamines, 7,12-dimethylbenz[a]anthracene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline 1-oxide and three biphenyl compounds. These results should be useful in relation to studies on the mechanism of inhibition of metabolic cooperation and on the relationship between this inhibitory activity and the tumor-promoting activity of various chemicals. (Author abstract) (12 Refs)

BIOASSAY BASED UPON ACTIVATION

76. APPLICATION TO BENZO(A)PYRENE FED RATS OF A PROPOSED SHORT-TERM IN VIVO CARCINOGEN SCREENING PROTOCOL (MEETING ABSTRACT).

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Department of Preventive Medicine, Cornell University, Ithaca, NY
Toxicologist; 1(1):36 1981

This study was undertaken to determine if induction of presumptive pre-cancerous lesions by benzo(a)pyrene (BP) could be predicted in a short-term treatment by demonstration of urinary mutagenesis and by increased concentration in the blood of the oncodevelopmental protein alpha fetoprotein (AFP). Existence of pre-cancerous lesions was confirmed by gamma glutamyl transpeptidase staining of liver sections from treated animals. Male weanling F344 Schf rats were fed semi-purified diets containing 0, 1, 100 or 1000 ppm BP with or without 0.05% sodium phenobarbital for six to thirteen wk. Blood was obtained at one to two wk intervals by cardiac puncture and plasma AFP levels were determined by sandwich type radioimmunoassay. Urine was collected for eight hr during the sixth wk of treatment. Glucuronidase-treated specimens were tested for mutagenesis in salmonella typhimurium strains TA98 and TA100 with and without microsomal activation. Liver specimens were stained for gamma glutamyl transpeptidase (GGT) activity and examined for presence of foci of altered cells. Those treatments resulting in elevated plasma AFP and mutagenic urine were associated with development of GGT-positive hepatic cell foci. This protocol could be applied early in the range finding phase of a carcinogenesis bio-assay to aid in selection of substances for long-term testing. (no Refs)

77. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS
Microbiological Associates, Bethesda, MD, 20816
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

78. MORPHOLOGIC ANALYSIS OF ATYPICAL ACINAR CELL LESIONS (AACL) INDUCED IN RAT PANCREAS BY 4-HYDROXYAMINOQUINOLINE-1-OXIDE (4-HAQO) (MEETING ABSTRACT).

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Newsletter Natl Pancreas Cancer Project; VI(2):48 1981

A metabolite and possible proximate carcinogen of 4-nitroquinoline-1-oxide, 4-HAQO, is both toxic and carcinogenic for pancreas. A single IV injection of 4-HAQO in male Wistar rats at a dose of 6 mg/kg body wt induced AACL in 100% of the animals. AACL could be classified histologically as zymogen-poor and zymogen-rich foci, and zymogen-rich nodules (gross-

ly visible). The zymogen-poor foci contained between 20-300 cells and rarely more than 500 cells. Cells in such foci were large, contained a large irregular nucleus with a prominent nucleolus, and a markedly basophilic cytoplasm with a few to small numbers of zymogen granules. By transmission electron microscopy (TEM) these cells showed markedly irregular lateral plasma membranes, a well developed rough endoplasmic reticulum (RER) and a few zymogen granules. Cells in zymogen-rich foci and nodules were arranged in acini which were larger than adjacent acini. The cells contained an intensely eosinophilic granular cytoplasm, and a large oval basophilic nucleus with a prominent nucleolus. By TEM, the cells showed a zymogen rich cytoplasm, RER and irregular lateral membranes. The mitotic and [3H] thymidine labeling indices respectively of both cell variants of AACL were as follows: eosinophilic cells, 2.75 and 23.2 basophilic cells 0.125 and 1.2 as compared to 0 and 1 for normal pancreatic acinar cells. These studies indicate that 4-HAQO induces at least 2 varients of AACL with different morphological features and growth potential. Their role in the pathogenesis of acinar cell adenomas and carcinomas remains to be elucidated. (no Refs)

79. USE OF CULTURED MAMMALIAN CELL TECHNIQUES TO EVALUATE THE TOXICITY OF CHEMICALS TRANSFORMED IN LABORATORY TERRESTRIAL ECOSYSTEMS (MEETING ABSTRACT).

Ross WD, Wininger MT, Hillan WJ
Monsanto Research Corporation, 1515 Nicolus Road, Dayton, OH, 45418
In Vitro; 17(3):224 1981

Mammalian cell culture techniques have been used to assess the acute cytotoxicity and potential health hazards of degradation products and metabolites resulting from the transformation of chemicals applied to or spilled on soil. Laboratory ecosystems, containing intact 10 cm x 70 cm soil cores have been designed for sampling leachates at 10-cm depth intervals along the vertical soil core. Stainless steel probes are inserted laterally into the soil and sampling boats containing adsorbents are positioned in the probes to recover organic compounds resulting from the transformation of test compounds applied at the soil core surface. Openings in the probes and sampling boats permit leachate containing the products to flow through. Three mammalian cell test methods were evaluated for determining acute cytotoxicity: (a) direct application of the adsorbent to an agar overlay culture containing D98S human and CHO-K1 cells; (b) application of a dimethylsulfoxide (DMSO) extract of the adsorbent to a mammalian cell clonal assay technique; and (c) bioautographic techniques in which thin-layer chromatography (TLC) of the soil leachates were applied to mammalian cell agar overlay culture plates. Bioactive spots indicating toxicity were detected by noting the slowing of growth or the death of the underlying cells. (no Refs)

REVIEWS AND OTHER RELEVANT STUDIES

80. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes known as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

81. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

Griffin MJ
Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

82. STRUCTURAL ASPECTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Glusker JP
Institute for Cancer Research, 7701 Burholme Avenue, Philadelphia, PA, 19111
Molecular Structure and Biological Activity: A Symposium on Biologically Active Molecules, (Twelfth Congress), August 26-28, 1981, Buffalo New York. International Union of Crystallography 89 pp., 1981.

The process of carcinogenesis by polycyclic aromatic hydrocarbons (PAH) involves the enzymatic 'activation' of the hydrocarbon to a diol epoxide and, it is presently believed, alkylation of DNA by this alkylating agent. The shape and size of the PAH is important. If it is too large or too small it is not as potent a carcinogen. The optimal size approaches that of a steroid or a base pair. This shape may also have significance in the interaction of the PAH with the hydroxylating enzyme. In addition, methyl substitution for hydrogen in the 'bay area' of a PAH, which characteristically causes distortions as a result of steric effects, often enhances carcinogenic activity. Studies in several systems have led to the conclusion that flatness is not a criterion for carcinogenicity and that total intercalation of the hydrocarbon cannot occur. The benzoflavone that inhibits the 'activation' process has been shown by x-ray studies to be nonplanar. Interactions between hydroxyl and epoxide groups in the same molecule may affect reactivity. The immediate aim of these studies is to determine what effects alkylation by an activated PAH can have on DNA. The structure of a nucleoside

alkylated by chloromethyl PAH has been studied and it is shown, as predicted, that the base and PAH portion lie almost perpendicular to each other. Some possible effects of such alkylation on DNA structure will be discussed. (no Refs)

83. THE NATURE OF THE RESISTANCE TO CYTOTOXICITY INDUCED IN HEPATOCYTES BY FEEDING A CARCINOGENIC REGIME OF AFLATOXIN B1 TO MALE FISCHER RATS (MEETING ABSTRACT).

Neal GE, Cabral JR
Toxicology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey, SM5 4EF, England
Toxicologist; 1(1):34 1981

Evidence is emerging that in the case of hepatocarcinogenesis by low-level administration of many different carcinogens, the irreversible carcinogenic change takes place at a time when the level of presumptive mutagenic lesions in the hepatic DNA is very much lower than that present following subcarcinogenic dosing. Aflatoxin B1 action clearly demonstrates this effect. It has been suggested that the mechanism is an enhanced repair of mutagenic lesions, but the kinetics of DNA binding of labelled aflatoxin are incompatible with this theory. Reduced binding of aflatoxin appears prinicipally to be due to enhanced detoxification of the activated toxin, and this has been demonstrated in vitro binding experiments. Induction of high levels of reduced glutathione and probably S-transferase enzymes appears to be responsible for the effect. These changes are principally, if not exclusively, located in foci of gamma glutamyl transferase positive cells. Evidence for the significance of these changes in terms of induction of preneoplastic lesions will be presented. (no Refs)

84. TOXICOLOGICAL CONSIDERATIONS FOR THE MEDICINAL CHEMIST.

Finch N
Pharmaceuticals Div., CIBA-Geigy Corporation, Summit, NJ, 07901
Med Res Rev; 1(4):337-372 1981

Toxicological considerations in the development of new drugs are reviewed. Expanding knowledge of drug metabolism and toxicology allows better direction of research into those compounds having the best chance of passing biological tests. One apparent mechanism of chemical carcinogenesis is attack by electrophilic molecules on DNA, nuclear proteins, or other cell components. A second mechanism is the induction of enzyme systems, particularly cytochrome P450 by a compound or its metabolites. Other toxicological problems include phospholipidosis, blood dyscrasias, effects on liver function, dermatological problems, hearing loss, and lupus syndrome. All of these should be considered in proposing new drugs for testing. A drug should have sufficient reversible toxicity to produce the desired effect without producing permanent damage to the patient. Quantitative structure-activity relationships and empirical approaches are reviewed. Structure-toxicity relationships of specific compounds are presented. In vivo transformation of drugs is discussed. (117 Refs)

85. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E
Merck Inst. for Therapeutic Res., West Point, PA, 19486
Mutat Res; 87(2):81-142 1981

The current literature on chemically induced specific locus mutations in the V79 Chinese hamster cell line are reviewed and evaluated. Characteristics of V79 cells, various genetic markers, and protocols for mutant induction by chemicals in the presence and absence of activation systems are described. The chemicals which were tested in V79 cells for mutagenic activity are listed. The usefulness of V79 cells for the screening of environmental chemicals which may be hazardous to humans is evaluated. Mutagenesis assays are discussed in relation to characteristics of the V79 cell line, genetic markers (hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus, reversion of HGPRT- mutants, ouabain-resistance, drug resistance, and auxotrophic, prototrophic and temperature-sensitive mutants) of V79 cells, and suggested and testing (toxicity and dose selection, standard mutagen treatment conditions, expression time, mutant selection, identification of phenotypic variants as presumptive genotypic variants, metabolic activation, cell-mediated mutagenesis, tissue homogenate-mediated mutagenesis, positive and negative controls, experimental design) protocols. Test performance is evaluated based on an analysis of the literature. The strengths and weaknesses of the V79 assay are considered. The role of the assay in mutagenicity and carcinogenicity testing programs is discussed. (162 Refs)

86. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASSAYS: A REPORT OF THE U.S. EPA'S GE NE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 87(2):143-188 1981

An assessment made by the United States Environmental Protection Agency Gene-Tox Program's Work Group on Mammalian cytogenetics of the clastogenic effects of chemicals in in vivo and in vitro mammalian assays based on 177 papers is presented. General considerations used in the interpretation of data included differential sensitivity of cells in different stages of the cell cycle, metabolic activation, suitability of protocols, and tabular presentation of data base. The protocols for testing and the chemicals reviewed for the bone marrow, spermatogonia, spermatocyte (treated spermatogonial stem cells and treated spermatocytes), oocytes and early embryo, in vitro cell culture assay, and peripheral leukocyte or lymphocyte assays are presented. Advantages and disadvantages of the cytogenetic assay systems are considered. (162 Refs)

87. SECOND ANNUAL REPORT ON NATIONAL CANCER INSTITUTE AND ENVIRONMENTAL PROTECTION AGENCY PROJECTS.

Department of Health and Human Services
Public Health Service, NIH, Bethesda, MD
Second Annual Report on National Cancer Institute and Environmental Protection Agency Projects. Bethesda, MD, National Cancer Institute, 384 pp., 1981.

Current projects underway under the auspices of the National Cancer Institute and the Environmental Protection Agency are described. Progress reports are presented for the following: a data base for chemicals identified in human biological media; in vivo analysis of UV-B-induced photooxidations; use of the hairless mice for carcinogenesis studies; chronic toxicity and carcinogenicity to rats and mice of chloroform in drinking water; the effects of carcinogens, mutagens, and teratogens on non-human (aquatic) species; the cost effectiveness of two types of personal UV-B dosimeters; the effects of varying doses of UV on mammalian skin; immunodiagnostic markers

for breast cancer; antigens on human lymphoid organs for the immunodiagnosis of leukemias and lymphomas; human epithelial cell metabolic activation systems for use with human cell mutagenesis; evaluation of the transformation assay using C3H 10T1/2 cells for use in screening chemicals for carcinogenic potential; national mortality data bases for environmental epidemiology; epidemiologic field studies on ecological relationships between specified toxic substances and cancer morbidity and mortality; an epidemiologic study of populations in Turkey previously exposed to hexachlorobenzene; a case control study of lung, pancreas, and stomach cancer in Southern Louisiana; support services for epidemiologic studies of lung cancer in communities with non-ferrous smelters; an epidemiologic study of the i ncidence of cancer as related to industrial emissions in the heavily industrialized parts of Contra Costa County in California; an environmental data base for New Jersey to be used in epidemiological studies; an etiologic study of respiratory cancer in coastal Texas; and completion of the NCI/NCHS cooperative study of 1972 mortality data. (no Refs)

88. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

A review is presented of the effects of air pollution on defense mechanisms of the body which may in turn account for differences in individual reactivity to such pollution. Some important findings relating to this problem follow: deterioration of lung clearance after inhalation of NO2 and lead chloride; damage to alveolar macrophages by air-borne particulates in vitro and in vivo; enhanced activation of C3 complement fraction under the influence of air pollutants; higher frequency of enlarged tonsils and lymph nodes, of pathogenic bacteria on tonsillar surfaces, and of relatively lower lysozyme concentrations in children living in urban or industrialized areas; decreased resistance to infections related to inhalation of O3 or a lead aerosol; immuno-suppressive effect of heavy metals and organic compounds; allergic reactions to many chemicals; detoxification and toxification, eg formation of ultimate carcinogens, and of organic molecules; induction or inhibition of benzo(a)pyrene metabolism by particulate extracts or by CO, NO2, and lead; deficiency of DNA-repair in disease conditions predisposing to development of cancer; tendency, in allergic subjects, to a relatively lower incidence of cancer; adaptation to the effect of CO and SO2. These facts, and others not cited, support a close connection between various defense mechanism, air pollution, and its effects on the human organism. (55 Refs) (In GER)

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1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

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3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlitttstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GEN E-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

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11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

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13. CANCER BIOLOGY.

Ruddon RW

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14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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Activation and Metabolism of Carcinogens

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APRIL, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

METABOLIC ACTIVATION OF CARCINOGENS

1. STUDIES ON THE MECHANISM OF CARCINOGENICITY OF DIETHYLSTILBESTROL: ROLE OF METABOLIC ACTIVATION.

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Food Cosmet Toxicol; 19(5):611-615 1981

Oxidative metabolism of diethylstilbestrol (DES), meso-hexestrol (HES), and E,E-dienestrol (E,E-DIES) is reviewed. DES is metabolized to a variety of oxidative metabolites along several pathways involving reactive intermediates. This observation, together with evidence that DES also produces genetic damage, raises the possibility that metabolic activation may be involved in DES carcinogenicity. The mechanism for organ-specific carcinogenicity of DES may involve formation of reactive metabolites that retain their estrogenicity and are thus accumulated in estrogen target organs. A second possibility may involve the preferential formation of reactive metabolites in target organs by specific metabolites. Metabolic oxidation of HES is confined to the aromatic and aliphatic portions of the molecule. E,E-DIES is oxidized at the aromatic ring and at the olefinic double bond, and there is no indication of aliphatic hydroxylation. These analogues may be useful for further clarifying the role of metabolic activation in the genetic toxicity and carcinogenicity of DES. (34 Refs)

2. THE ACTIVATION OF AFLATOXIN B1 IN LIVER SLICES AND IN BACTERIAL MUTAGENICITY ASSAYS USING LIVERS FROM DIFFERENT SPECIES INCLUDING MAN.

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Carcinogenesis; 2(10):1063-1068 1981

Activation of aflatoxin B1 (AFB1) was compared in two in vitro systems: binding to DNA in liver slices incubated with 14C- or 3H-AFB1 and in standard bacterial mutation systems using 9000 x gravity supernatant (S-9) fractions from uninduced livers for activation. The results were compared in several rodent species in an effort to correlate them with known trends in carcinogenicity. Covalent binding of 14C-AFB1 to DNA from liver slices showed the order rat greater than hamster greater than mouse. Phenobarbitone pretreatment of rats decreased binding, and binding of aflatoxin G1 (AFG1) was less than that of AFB1. These findings all were correlated with relative susceptibility to AFB1-induced hepatocarcinogenesis. An exception to this trend was the similar level of binding found in male and female rat livers. Levels of 3H-AFB1 binding to DNA in human liver biopsies ranged from 0.7-8.5 nanog AFB1/mg DNA, which was similar to the range seen in the mouse and hamster. Mutagenicity data did not correlate with carcinogenicity in relation to species differences, as the efficiencies of livers from the three species for activating AFB1 mutagenicity were hamster greater than rat greater than mouse. AFG1 mutagenicity generally was markedly less than that of AFB1 when activated by rat liver S-9. The correlation between AFB1 binding to DNA in liver slices in various rodent species and susceptibility to AFB1 hepatocarcinogenesis and its modification in the rat by phenobarbitone suggests that these differences are related to differences in metabolic activation of AFB1 to its reactive species, its subsequent detoxification, and macromolecular interaction. (30 Refs)

3. METABOLIC ACTIVATION OF AFLATOXIN B1 BY LIVER TISSUE FROM MALE FISCHER F344 RATS OF VARIOUS AGES.

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Mech Ageing Dev; 17(2):163-171 1981

The effect of aging on the ability of the liver to activate chemical procarcinogens was studied using 12-, 18-, and 27-mo-old male Fischer F344 rats. The cytochrome P-450 content of the S9 and microsomal fractions of the liver decreased approx 30% between 12 and 18 mo of age. The structural conformation of cytochrome P-450 in microsomes from 12-, 18-, and 27-mo-old rats was studied using electron-spin resonance spectroscopy. An age-related decrease in the amount of cytochrome P-450 ferric iron in the liver microsomes was observed. The conversion of the chemical procarcinogen aflatoxin B1 to mutagenic compounds by the S9 and microsomal fractions of liver was measured using the Salmonella typhimurium bioassay. A 40-50% decrease in the metabolic activation of aflatoxin B1 was observed between 12 and 18 mo of age. However, the activation of aflatoxin B1 did not change after 18 mo of age. The age-related decrease in the activation of aflatoxin B1 by liver appears to be due to a decrease in the metabolic activity of the mixed-function oxidase system. (Author abstract) (27 Refs)

4. SPECIFICITY OF RABBIT PULMONARY CYTOCHROME P-450 ISOZYMES IN THE ACTIVATION OF SEVERAL AROMATIC AMINES AND AFLATOXIN B1.

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Mol Pharmacol; 20(3):662-668 1981

The activation of 2-aminoanthracene (2-AA), 2-aminofluorene (2-AF), 2-acetylaminofluorene (2-AAF), and aflatoxin B1 (AFB1) by rabbit pulmonary and hepatic preparations was studied using the Salmonella strain TA98. In experiments with either antibodies to specific cytochrome P-450 isozymes or monooxygenase systems reconstituted from purified enzymes, the observed activities were related to the relative concentrations and activities of these isozymes. Rabbit pulmonary and hepatic S16 fractions produced mutagenic products from 2AA, 2AAF, and 2AF, and AFB1. The hepatic fraction was more active, with regard to the amount of S16 protein required to produce a given number of revertants, with 2AA (up to 2x), 2-AAF (2.5-5x), and AFB1 (5x), whereas the pulmonary fraction was more active with 2AF (up to 2x). On the basis of cytochrome P-450 content, the activity of the pulmonary fraction was greater than or equal to that of the hepatic fraction. For a given substrate concentration, a comparison of the amounts of cytochrome P-450 required for equivalent activity showed that the pulmonary microsomal fraction was 3-4, 20-25, and 25-30x more active than the hepatic fraction in the formation of mutagenic products from 2AAF, 2AA, and 2AF, respectively. With AFB1, similar activities were obtained with both microsomal fractions, the pulmonary fraction being slightly more active. The promutagens 2AA, 2AF, and 2AAF were substrates for both P-450II and P-450LM4 but were inactive with P-450I. P-450LM1 showed greater activity with 2AAF, however, P-450II gave 10-20 times more mutagenic activity with 2AA and 2AF than did P450LM4. With AFB1, only incubations containing P-450I gave a significant increase in the number of revertants. Experiments with antibodies against P-450I and P-450II confirmed these findings. (29 Refs)

5. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
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Sci Tech Aerosp Rep; 19(18):2533 1981

An environmental carcinogen, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

6. EFFECTS OF FLUORINE SUBSTITUTION ON THE TUMOR INITIATING ACTIVITY AND METABOLISM OF 5-HYDROXYMETHYLCHRYSENE, A TUMORIGENIC METABOLITE OF 5-METHYLCHRYSENE.

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Carcinogenesis; 2(10):1027-1032 1981

Tumor-initiating activity of 5-methylchrysene (5-MeC) on mouse skin was compared with that of a major 5-MeC metabolite, 5-hydroxymethylchrysene (5-HOMeC). After an initiating dose of 30 ug, with promotion by tetradecanoylphorbol acetate, 5-HOMeC induced skin tumors in 90%, with 9.5 tumors/mouse. 5-MeC resulted in 75% incidence of skin tumors with 6.2 tumors/mouse. The tumorigenic activities after a 10 ug initiating dose were: 5-HOMeC, 45% incidence and 2.6 tumors/mouse; 5-MeC, 55% incidence and 5.6 tumors/mouse. The compound 6,hydroxymethylchrysene was inactive. The tumor initiating activities of two monofluoro derivatives also were investigated to elucidate the mechanism of 5-HOMeC activation. 7-Fluoro-5-hydroxymethylchrysene (7-F-5-HOMeC) was as tumorigenic as 5-HOMeC, whereas 3-fluoro-5-hydroxymethylchrysene (3-F-5-HOMeC) was significantly less tumorigenic. The inhibition of tumorigenicity by substitution of fluorine at the 3-position, but not the 7-position of 5-HOMeC is analogous to previously described results with 5-MeC and suggests a similar mechanism of activation for both compounds. Metabolites formed upon incubation of 5-HOMeC with cofactors and the 9,000x gravity supernatant from Aroclor pretreated rats were separated by high pressure liquid chromatography. The 1,2-dihydrodiol and 7,8-dihydrodiol of 5-HOMeC were identified. The major phenolic metabolite was 1-hydroxy-5-hydroxymethylchrysene. In the in vitro metabolism of 7-F-5-HOMeC under the same conditions, 1,2-dihydrodiol was identified but not 7,8-dihydrodiol. In the metabolism of 3-F-5-HOMeC, oxidation in the 1-4 ring was inhibited relative to that observed in the metabolism of 5-HOMeC. These results suggest that 5-HOMeC is activated primarily through formation of its 1,2-dihydrodiol. (27 Refs)

7. FORMATION OF TISSUE-BOUND N'-NITROSONORNICOTINE METABOLISM BY THE TARGET TISSUES OF SPRAGUE-DAWLEY AND FISHER RATS.

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Carcinogenesis; 2(10):959-963 1981

The way in which N'-[14C]nitrosonornicotine (NNN) selectively induces tumors in the nasal cavity and esophagus in Sprague-Dawley and Fisher rats was investigated. No major differences in distribution of radioactivity was seen in the two strains. In vivo and in vitro autoradiographic studies following iv injection of 14C-NNN demonstrated localization of tissue-bound metabolites in the mucosa of the nasal cavity, esophagus, tracheo-bronchial tree, and tongue. High levels of unbound radioactivity were found in Zymbal's gland and submaxillary, preputial, lacrimal, and tarsal glands. In vitro experiments in which tissue slices were incubated with 3 uM 14C-NNN, demonstrated marked formation of tissue-bound NNN metabolites by nasal mucosa, liver, and esophagus. Liver tissue also formed bound NNN metabolites, but to a lesser extent than nasal mucosa, whereas levels of bound metabolites in esophagus cultures were almost undetectable. The results suggest that in situ metabolic activation of NNN plays an important role in the pathogenesis of NNN-induced tumors. (13 Refs)

8. METABOLIC ACTIVATION OF A TRYPTOPHAN PYROLYSIS PRODUCT, 3-AMINO-1-METHYL-5H-PYRIDO(4,3-B)INDOLE (TRP-P-2) BY ISOLATED RAT LIVER NUCLEI.

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Cancer Lett; 14(3):261-266 1981

The abilities of nuclei and microsomes to convert 3-amino-1-methyl-5H-pyrido[3,4 -b]indole (Trp-P-2) to an active mutagen were compared. Nuclei from polychlorinated biphenyl or methylcholanthrene-treated rats activated Trp-P-2 and caused a greater number of revertants in the Salmonella mutation test than nuclei isolated from phenobarbitol-treated or non-treated rats. Similar pretreatment effects were observed with microsomal activation. (17 Refs)

9. THE INFLUENCE OF DISULFIRAM AND OTHER INHIBITORS OF OXIDATIVE METABOLISM ON THE FORMATION OF 2-HYDROXYETHYL-MERCAPTURIC ACID FROM 1,2-DIBROMOETHANE BY THE RAT.

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Biochem Pharmacol; 30(21):2983-2987 1981

The mercapturic acid derivative, N-acetyl-S-2-hydroxyethyl-L-cysteine, is a major metabolite of 1,2-dibromoethane in vivo. This compound can be formed via two pathways, both involving a potentially dangerous reactive intermediate. One way involves the intermediacy of bromoacetaldehyde, formed by microsomal oxidation, followed by loss of hydrogen bromide. The second pathway, direct conjugation of 1,2-dibromoethane with glutathione, gives rise to S-2-bromoethyl glutathione. Using several inhibitors of microsomal mixed function oxidases, it was found that under these conditions about 10% of the mercapturic acid derivative formed via direct conjugation. Disul-

firam, an inhibitor of aldehyde dehydrogenases, but also of microsomal oxidation, also markedly inhibits the excretion of the mercapturic acid, after administration of a single high dose (1 g/kg) or upon chronic treatment with a low dose (50 mg/kg). The inhibitory effect is max after 10 days of chronic treatment. Administration of large amounts of 1,2-dibromoethane (greater than 0.20 nmole/rat) following a single lower dose of disulfiram (125 mg/kg) also leads to a lower excretion of mercapturic acid metabolite, a phenomenon associated with a decrease in cytochrome P-450 levels. From these results it is concluded that the enhanced carcinogenic effect of the combination disulfiram (chronic)/1,2-dibromoethane is not caused by bromoacetaldehyde, since its formation is completely inhibited under these conditions, but by S-2-bromoethyl-glutathione, although a role for 1,2-dibromoethane itself cannot be excluded. (Author abstract) (27 Refs)

OTHER METABOLISM OF CARCINOGENS

10. NEW PATHWAYS FOR CHLORINATED DIOXINS.

Hay A
Dept. Chemical Pathology, Univ. Leeds, Leeds, England
Nature; 294(5841):514-515 1981

Although 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is itself active, approx 1% of TCDD is metabolized. TCDD metabolism has been observed in vitro in Golden Syrian hamster hepatocytes. A reaction scheme for the metabolism of TCDD in rats and dogs is presented. Dynamic equilibrium between adipose and other tissues to maintain blood TCDD levels has been postulated for some animals. In humans, the TCDD blood levels are low but long-lasting. The metabolism of other polychlorinated compounds is discussed with reference to the Yusho I and II cases. Carcinogenic risk associated with TCDD is discussed. (no Refs)

11. COMPARATIVE METABOLISM OF 2,6-DIMETHYLNITROSOMORPHOLINE IN RATS, HAMSTERS, AND GUINEA PIGS.

Underwood B, Lijinsky W
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):54-58 1982

The metabolism of N-[3,5-3H]nitroso-2,6-dimethylmorpholine (NDMM) was studied in female Sprague-Dawley rats, Syrian golden hamsters, and guinea pigs. NDMM induces tumors in the esophagus in rats, pancreatic cancer in hamsters, and hemangioendothelial tumors of the liver in guinea pigs. An intragastric dose of NDMM (2 mg, 2 uCi/animal) was rapidly distributed throughout the tissues of both the rat and hamster, with no apparent accumulation of radioactivity in any one tissue. At low dose levels, NDMM was metabolized rapidly by both species. The hamster appeared to metabolize the compound faster than did the rat or guinea pig. An appreciable amount of radioactivity was excreted in the urine in all three species after 8 hr: approx 54% in the hamster; 39% in the rat; and 30% in the guinea pig. During the first 24 hr, only a small percentage of the radioactivity excreted by the hamster, rat, and guinea pig was NDMM (0.8, 2, and 0.5% respectively). High-pressure liquid chromatography analysis of urine collected 24 hr after administration revealed 12 metabolites. Although the urinary metabolites appeared to be similar in all three species, one large difference was the presence of a major urinary metabolite in hamster urine, which was absent or present in only small quantities in the rat and guinea pig. The guinea pig urine also had relatively more radioactivity present in one major fraction than did the hamster or rat. (Author abstract) (22 Refs)

12. COMPARISON OF THE IN VITRO METABOLISM OF N-NITROSOHEXAMETHYLENEIMINE BY RAT LIVER AND LUNG MICROSOMAL FRACTIONS.

Hecker LI, McClusky GA
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 42(1):59-64 1982

The in vitro metabolism of N-nitrosohexamethyleneimine by lung and liver microsomes and cytosol from uninduced male Fischer rats is described. Metabolites produced by both organs appeared to be identical. the liver subcellular fractions had a lower Km (0.6 mM) than did lung fractions (3 mM) and metabolized 2.5 to 5x as much nitrosamine per mg protein. Our results, together with those from our earlier studies, indicate that, as the size of the carbon ring increases from nitrosopyrrolidine to nitrosohexamethyleneimine lung microsomes had an increased affinity for the cyclic nitrosamines; there was only a small ef fect with liver enzymes. This suggests that microsomal enzymes that metabolize cyclic nitrosamines in rat livers and lungs are not the same. the first stable alpha-hydroxylation product, 6-hydroxyhexanal, was not detected in reactions involving microsomes alone. Apparently, this compound is rapidly converted to 1,6-hexanediol by liver or lung microsomes. The presence of cytosol was needed for the full conversion of these metabolites to epsilon-hydroxycaproate and max alpha-hydroxylation activity. Epsilon-Aminocaproate was always found in direct proportion to the hydroxyacid, suggesting that both acids arise from the same alpha-hydroxylation event by different breakdown mechanisms. Beta- and gamma-hydroxynitrosohexamethyleneimine were not metabolized significantly by rat liver enzymes and thus, in this species, may be 'detoxification products' of N-nitrosohexamethyleneimine. (Author abstract) (20 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. EFFECTS OF BUTYLATED HYDROXYANISOLE ON THE ARYL HYDROCARBON HYDROXYLASE OF RATS AND MICE.

Yang CS, Sydor W, Martin MB, Lewis KF
Dept. Biochemistry, CMDNJ-New Jersey Medical Sch., Newark, NJ, 07103
Chem Biol Interact; 37(3):337-350 1981

The effects of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on the aryl hydrocarbon hydroxylase (AHH) activities in the liver, lung and skin of rats and mice have been studied to examine the possible mechanisms of the anticarcinogenic actions of these compounds. Both compounds inhibit the hydroxylase activities of hepatic microsomes and nuclei, with BHA a more potent inhibitor than BHT. The AHH of lung microsomes is inhibited to a lesser extent by BHA and BHT than that of the liver. The AHH activities of both liver and lung microsomes become less susceptible to the inhibition after pretreatment of the animals with 3-methylcho-

anthrene (MC) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but phenobarbital (PB) pretreatment does not produce such an effect. In skin homogenates, however, the AHH activities of control rats and mice are not inhibited by BHA and BHT. The only skin sample which is inhibited by BHA and BHT is that from TCDD-pretreated mice. It has been established that the extent of inhibition with different samples is related to the concentration of BHA in the incubation but not to the amounts or specific activities of microsomes used. Double reciprocal plots suggest that BHA exerts a mixed inhibition on the hydroxylase of liver microsomes with Ki of 7.7 uM. Analysis of the metabolites of benzo[a]pyrene (BP) shows that BHA inhibits the formation of various metabolites uniformly without changing the regioselectivity of the enzyme system. The mechanism of inhibition has also been studied with a reconstituted AHH system consisting of cytochrome P-450 (P-450), reductase and phospholipid. The system with P-450 isol ated from PB-induced microsomes is inhibited to a much greater extent than that with MC-induced P-450. The results indicate that the inhibitory action of BHA is dependent on the species of the animal, tissue types and treatment with inducers. (Author abstract) (42 Refs)

14. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
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Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

15. ROLE OF NUTRITIONAL FACTORS IN REALIZATION OF BIOLOGICAL EFFECTS OF XENOBIOTICS.

Sharmanov TS
Kazakh Branch, Inst. Nutrition, Alma-Ata, USSR
Vopr Pitan; (5):51-57 1981

The role of nutritional factors in the metabolism of pesticides, nitrosamines, and aflatoxins is reviewed. Nitrites present in canned meat or fish can react with exogenous amines to yield carcinogenic nitroso compounds. Dietary deficiency of vitamin C and essential amino acids enhanced the carcinogenic activity of N-nitrosopyperidine in guinea pigs. Deficiency of the essential amino acids and retinol enhanced the incidence of aflatoxin B1-induced tumors in rats. (33 Refs) (In RUS)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

16. STRUCTURE-MUTAGENICITY ANALYSI CHO/HGPRT SYSTEM.

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Food Cosmet Toxicol; 19(5):617-621 1981

A mutational system which affects hypox phosphoribosyl transferase (HGPRT) activity ster ovary (CHO) cells, the CHO/HGPRT sy to study the structure-mutagenicity of 10 carci ing agents and 6 platinum(11) compounds. Cyto genic effects of the alkylating agents decreased size of the alkylating group. When the relati DNA alkylation and mutation at the hgprt loc N-methylurea (MNU) and N -nitroso-N-ethylu studied, MNU, on an equimolar basis, had 35 activity of ENU but only 3x the mutagenic acti of DNA by ENU resulted in greater than 4x mutagenic lesions than did methylation by MN diammine platinum(11) was the most mutagen platinum(1)chloroammines, while its steric is form, was non-mutagenic. Mutagenicity and cy in their reactivity of DNA binding. The mutag the cis isomer as a function of treatment co 2400x that of the trans isomer. However, the c only 3x more to cellular DNA than did the tr mutant yield per molecule bound to DNA wa the cis than for the trans isomer. Cytotoxicity was a factor of 9 greater for the cis than for t These studies demonstrate that both the quanti DNA adducts affect mutagenicity and cytotox HGPRT system is useful for studying genetic cology and for relating molecular paramete mutagenic and cytotoxic activities. (26 Refs)

17. ETHANOL- OR ACETONE-PRETREATM STRONGLY ENHANCES THE BACTERIAL MUTAGENICITY OF DIMETHYLNITROSA ASSAYS MEDIATED BY LIVER SUBCELLU FRACTION, BUT NOT IN HOST-MEDIATE

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Carcinogenesis; 2(10..1057-1061 1981

The effect of acetone or ethanol pretreatmen methylnitrosamine (DMN) mutagenicity in ho cellular fraction-mediated assays was investiga typhimurium TA 92 was used in both the in vi assay and in the in vivo host-mediated assay more sensitive than TA 1535, TA 100, or T WP2 uvrA and because it possesses an intac layer. Pretreatment of C57BL/6J mice with moles of acetone or 30-60 millimoles of ethan tiated DMN mutagenicity in S9 mix-mediated DMN concentrations (100 uM), greater than tants were induced with S9 mix from acet than with S9 mix from controls. Ethanol ha weaker, effect. In the host-mediated assay, DM mutagen, but this effect was not enhanced with either acetone or ethanol. In general, slightly lower in acetone-pretreated animals tha

possible explanation for the differences observed in vitro and in vivo may be that in vitro the activity of the dilute metabolizing system is limiting for the activation of DMN, whereas in vivo DMN is completely metabolized in both induced and noninduced animals. (16 Refs)

18. MUTAGENICITY PATTERNS RESULTING FROM THE REACTION OF NITRITE WITH ICR-170.

de Flora S, Zanacchi P, Camoirano A, Bennicelli C
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Mutat Res; 103(1):13-17 1982

ICR-170, 2-methoxy-6-chloro-9-(3-[ethyl-2-chloroethyl] aminopropylamino) acridine.2HCl reacted with nitrite in an acidic environment to form a mutagenic derivative. Suitable soln of sodium nitrite were preincubated, either separately or mixed together, with 5 ml of human gastric juice or 0.15 M NaCl adjusted to various pH values. After 60 min at 37 C, 1 ml of 0.2 M phosphate-buffered saline, pH 7.4, was added. The resulting mixtures (0.5 ml/plate) were assayed in the plate incorporation test using various Salmonella his- strains. All the strains except TA1535 were reverted by ICR-170. TA1537 was most sensitive, a finding typical for acridine derivatives. Mutagenicity of TA1537 and of the other positive strains (TA 1538, TA98, and TA100) was increased by rat liver S9 fractions. The metabolic effect was less pronounced than previously reported for the same compound lacking an ethyl group (ICR-191). Direct frameshift activity of ICR-170 decreased in all positive strains after its reaction with nitrite. Such an activity was replaced by an S9-requiring mutagenic response in TA1538, TA98, and TA100; the response correlated with the amounts of both ICR-170 and nitrite. The study suggests that nitrosation of ICR compounds occurs at the only site where ICR-170 and ICR-191 are different, ie, at the terminal nitrogen of the nitrogen-mustard moiety. (10 Refs)

19. ENHANCEMENT OF BENZO(A)PYRENE INDUCED SISTER CHROMATID EXCHANGES AS A CONSEQUENCE OF GLUTATHIONE DEPLETION IN VIVO.

Bayer U, Younes M, Siegers CP
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Toxicol Lett; 9(4):339-343 1981

The effect of decreased hepatic glutathione (GSH) concentration on sister chromatid exchange (SCE) in vivo in the bone marrow of Chinese hamsters induced by 3,4-benzo(a)pyrene (BaP) was examined. SCE were studied in differentially stained bone marrow after sc implantation of 50 mg bromodeoxyuridine, ip injection of phorone (125 or 250 mg/kg body wt) or olive oil, and injection of BaP (50 or 100 mg/kg body wt). Induction of SCE by BaP after pretreatment with 125 mg/kg phorone increased to an av 5.9 (50 mg/kg BaP) and 7.0 (100 mg/kg BaP) SCE/cell. Pretreatment with 250 mg/kg phorone resulted in SCE values of 6.8 (50 mg/kg BaP) and 7.6 (100 mg/kg BaP). Hepatic GSH content and GSH S-transferase activities were also studied after injection of phorone (125 or 250 mg/kg body wt) or olive oil. Pretreatment with 125 mg/kg phorone led to a decrease in the GSH content to 1.2 micromole/g liver but had no significant effect on GSH S-transferase activities. Pretreatment with 250 mg/kg phorone gave no further effect. Apparently the amount of GSH available is one factor responsible for the degree of detoxication of BaP. The higher SCE frequency in the absence of GSH is probably a consequence of an increased amount of reactive, mutagenic BaP metabolites. (18 Refs)

20. INDUCTION OF GENE MUTATIONS BY BENZ(A)PYRENE DURING METABOLIC ACTIVATION.

Pashin IuV, Bakhitova LM
Inst. General Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(9):327-329 1981

The mutagenic activity of benz(a)pyrene (BP) was studied in Chinese hamster diploid cell line V-79. Incubation of the cell culture in media containing BP (5-25 ug/ml) and microsomal activating mixture resulted in a dose-dependent increase in the yield of gene mutations. (13 Refs) (In RUS)

21. CYTOTOXICITY AND MUTAGENICITY OF DINITROTOLUENES IN CHINESE HAMSTER OVARY CELLS.

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Mutat Res; 103(1):53-59 1982

Technical grade dinitrotoluene (DNT), a mixture composed predominantly of 2,4-and 2,6-DNT but containing lesser amounts of 2,3-, 2,5-, 3,4-, and 3,5-DNT, was tested for mutagenicity using the Chinese Hamster Ovary/Hypoxanthine-Guanine Phosphoribosyl Transferase system. Induction of mutation to 6-thioguanine (TG) resistance was tested in the presence and absence of microsomal preparations (PMS) from rats pretreated with the mixed function oxidase inducer Aroclor 1254. Marked differences in isomeric cytotoxicity were observed. However, neither technical grade DNT nor any of the purified isomers resulted in a significant increase in the TG-resistant fraction of surviving cells with or without PMS. (19 Refs)

22. MUTAGENICITY OF GLYCEROL CHLOROHYDRINES AND OF THEIR ESTERS WITH HIGHER FATTY ACIDS PRESENT IN PROTEIN HYDROLYSATES.

Silhankova L, Smid F, Cerna M, Davidek J, Velisek J
Dept. Biochemistry and Microbiology, Inst. Chemical Technology, 166 28 Prague 6, Czechoslovakia
Mutat Res; 103(1):77-81 1982

Mutagenicity of the glycerol chlorohydrines 3-chloro-1,2-propanediol (3CP) and 1,3-dichloro-2-propanol (1,3DP), and of their esters with palmitic and oleic acids, was tested with strains of Salmonella typhimurium and Escherichia coli. 3CP and 1,3DP caused base substitutions in S typhimurium TA1535 with and without metabolic activation. Metabolic activation in vitro with S9 mix did not influence the mutagenic effect of non-toxic concentrations of the glycerol chlorohydrines, but it led to a strong increase in the amount of mutants with those chlorohydrine concentrations causing strong suppression of background growth without metabolic activation. Difference in the growth of wild-type and repair-deficient strains of E coli was observed only for 1,3DP with S9 mix. Esters of both 3CP and 1,3DP with fatty acids had smaller mutagenic effects than unesterified compounds. (16 Refs)

23. SYNTHESIS AND MUTAGENIC ACTIVITY OF ALKYL DERIVATIVES OF 2-AMINO-9H-PYRIDO[2,3-B]INDOLE.

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Agric Biol Chem; 45(9):2031-2035 1981

Synthesis and mutagenic activity of 2-amino-3-methyl-9H-pyrido[2,3-b]indole (MeAC) and other alkyl derivatives of 2-amino-9H-pyrido[2,3-b]indole (AC) were investigated; identification of 2-amino-3-ethyl-9H-pyrido[2,3-b]indole (EtAC) in the pyrolysate of soybean globulin is reported. Ames tests and recassays gave similar results with MeAC and AC, showing substantially the same mutagenic activity as MeAC and EtAC obtained from soybean globulin. An increase in number of carbons in the alkyl group was accompanied by a decrease in mutagenic activity. Activation of the C-2 amino group by liver-homogenate may have been hindered sterically by a neighboring substituent, as possibly was the binding of DNA and the activated compound. (11 Refs)

24. MUTAGENIC ACTIVITY OF ISONIAZID AND ITS METABOLITES IN DIFFERENT TEST SYSTEMS.

Menon MM, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 19(10):939-942 1981

The mutagenic activity of isoniazid (INH) and its metabolites was examined using the Ames test system employing Salmonella typhimurium strains as well as two in vivo mammalian test systems (dominant lethal test and testicular DNA biosynthesis inhibition test). Possible prevention of mutagenic effects of INH using INH antitoxicants was also studied. INH without rat liver S9 mixture was mutagenic towards TA 100 and TA 1535. INH was not mutagenic to TA 92 or TA 98. Use of para-amino salicylic acid with INH significantly increased the number of revertants obtained. Two INH hydrazine metabolites, hydrazine sulfate (HS) and monoacetyl hydrazine (MAH), were mutagenic, HS for strains TA 92, TA 100, and TA 1535, and MAH for TA 100 and TA 1535. Negative results were obtained with diacetyl hydrazine and acetyl isoniazid. Of the three chemicals found to be positive, HS showed max mutagenicity in the presence of S9. Folic acid and pyridoxine slightly inhibited INH mutagenicity. The response of INH and HS was negative in the dominant lethal test. DNA synthesis in mouse testis was inhibited by INH, HS, MAH, and acetyl INH. It was concluded that the Ames test and the testicular DNA synthesis inhibition test show a good correlation in displaying mutagenicity of INH, HS, and MAH. (21 Refs)

25. THE ACTION OF TRANSITION METALS ON THE GENOTOXICITY OF SIMPLE PHENOLS, PHENOLIC ACIDS AND CINNAMIC ACIDS.

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Cancer Lett; 14(3):251-260 1981

The capacity of several phenolic compounds to induce chromatid breaks and exchanges in Chinese hamster ovary cells, and the modulating effect of the transition metals Cu++ and Mn++ on the clastogenicity of phenolics were examined. All dihydroxylated and trihydroxylated phenolics induced chromatid breaks and exchanges. Addition of S9 mixture or transition metals enhanced clastogenicity of some phenolics but reduced it in others. (35 Refs)

26. CONVERSION OF CHLORINATED NITROBIPHENYL ETHERS AND THEIR DERIVATIVES TO MUTAGENS BY WHITE-SPOTTED CHAR, SALVELINUS LEUCOMAENIS, LIVER HOMOGENATE.

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Bull Jpn Soc Sci Fish; 47(2):243-250 1981

Mutations were induced by p-nitrobiphenyl ether, its chlorinated forms, and their nitroso derivatives in a Salmonella typhimurium assay without liver homogenate. Liver homogenate from the white-spotted char increased mutagenicity of the compounds slightly and greatly increased the mutagenicity of amino derivatives. (23 Refs)

27. EFFECT OF CALCIUM PHOSPHATE AND ALUMINA C GAMMA GELS ON THE MUTAGENICITY AND CYTOTOXICITY OF DIMETHYLNITROSAMINE AS STUDIED IN THE CHO/HGPRT SYSTEM.

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Mutat Res; 84(1):147-156 1981

The effects of calcium phosphate and alumina C gamma gels in the S9 activation system on the cytoxicity and mutagenicity of dimethylnitrosamine (DMN) were studied in the Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyl transferase system. The calcium phosphate gel in the Ca/Mg-S9 mix was essential in potentiating the mutagenic activity of DMN. Varying amounts of CaCl2 were added to the Mg-S9 salts before adding S9 protein to determine whether the cytotoxic and mutagenic effects of DMN were due to Ca++ in the Ca/Mg-S9 mix. Increasing amounts of CaCl2 in the Mg-S9 mix made up in phosphate buffer caused increased cell killing and mutant induction; the max was observed at a Ca++ concentration of 10 milliM. Increasing concentrations of commercial preparations of calcium phosphate and tricalcium phosphate gels also increased cytotoxicity and mutagenicity of DMN. Alumina C gamma gel in Mg-S9 mix was just as effective as calcium phosphate gel in activating DMN. The cytotoxicity and mutation frequency of DMN were almost identical to those obtained with calcium phosphate gel. Diethylaminoethyl cellulose caused some increase in DMN-induced cytotoxicity but not -mutagenicity. Increasing the contact time between the S9 protein and the S9 salts increased the efficacy with which the S9 mix activated DMN; this was indicative of an adsorptive process by calcium phosphate gel. The results indicated that calcium phosphate or alumina C gamma gels can mimic the effects of cytosolic factors on the microsomes or by concentration of demethylase activity around the cells. (21 Refs)

28. INVESTIGATIONS ON THE MUTAGENICITY OF PRIMARY AND SECONDARY ALPHA-ACETOXYNITROSAMINES WITH SALMONELLA TYPHIMURIUM: ACTIVATION AND DEACTIVATION OF STRUCTURALLY RELATED COMPOUNDS BY S-9.

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Carcinogenesis; 2(10):991-997 1981

Mutagenicity of 12 primary and secondary alpha-acetoxynitrosamines (AANs) was investigated to elucidate the influence of structure on the extent of their biologic activity. Aldehydes

presumably arising after AAN cleavage were nonmutagenic in Salmonella typhimurium strain TA 1535. After hydrolysis, AANs were mutagenic, indicating that AAN mutagenicity is caused mainly by the alkylating species generated after cleavage of the acetates and not by the corresponding aldehydes. More stable primary AANs were less mutagenic at equimolar concentrations than the respective secondary compounds. Addition of S-9 mix caused both activation and deactivation in an unexpected structure-related pattern: An exactly opposite influence of S-9 components on mutagenicity was observed for each pair of primary and secondary AANs containing the same alkylating species. Pairs of compounds with both methylating and ethylating properties were influenced differently by addition of S-9 than those with propylating or butylating properties. This demonstrates how different chemical properties of intermediate forms may influence biologic activity of otherwise similar compounds. (28 Refs)

29. CYTOTOXIC AND MUTAGENIC EFFECTS OF STERIGMATOCYSTIN ON CULTURED CHINESE HAMSTER CELLS.

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Carcinogenesis; 2(10):945-949 1981

Cytotoxicity and mutagenicity of sterigmatocystin (STC) on cultured Chinese hamster cells were investigated in the presence and absence of a metabolic activation system. STC, when applied directly to V79 cells, was cytotoxic and induced 8-azaguanine-resistant mutations in a dose- and time-dependent manner. Effects of STC were enhanced markedly by 1%, 5%, or 20% S15 (polychlorinated biphenyl-induced rat liver microsomes) and other cofactors. In the presence of 1% S15, STC concentration required to induce cytotoxicity was approx 20x less than that required when S15 was applied directly; 1% STC was more cytotoxic and more mutagenic than either 5% or 20% STC. Analysis on the basis of equitoxic levels demonstrated that there was little difference in the degree of mutagenicity induced by direct treatment with STC and treatment with STC in the presence of S15. The effects of STC were enhanced in proportion to the duration of the treatment period. Treatment for shorter periods, however, was more effective than that for longer periods. The decreased effectivness was not attributable to instability of STC. (21 Refs)

30. MUTAGENICITY OF OIL-SHALE ASH.

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Mutat Res; 103(1):5-12 1982

Three oil shale samples were analyzed for mutagenicity in four test systems after extraction with solvents. In Salmonella typhimurium, extracts were highly mutagenic with Ames his reversion and ara-resistant systems; mutation induction was independent of metabolic activation and was of the frameshift type. The extracts showed substantial killing effect, but they failed to induce ad-3 reversion in Neurospora crassa, gene conversion and mitotic crossing-over in Saccharomyces cerevisiae, or TGr mutation in cultured CHO cells. (14 Refs)

31. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

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Food Cosmet Toxicol; 19(5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform ($r = 0.206$). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

32. FLAVONOIDS, MUTAGENS, AND CITRUS.

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ACS Symp Ser; 170:43-59 1981

Data on the mutagenicity of flavonoids are reviewed. Of all classes of flavonoid s, mutagenicity has been demonstrated only for some of the flavonols. Quercetin had the highest mutagenic activity in the Ames test in Salmonella typhimurium. The validity of the Ames test, however, depends on the activating agents used. Flavonols occur in almost all higher plant tissues and are common in human diets. The most common flavonols are quercetin and kaempferol, which almost always occur in the form of glycosides, which are nonmutagenic. Metabolism of quercetin glycosides is probably carried out along several pathways by intestinal microflora. Any occurrence of mutagenic quercetin aglycone is probably fleeting at most. Animal feeding studies of quercetin carcinogenicity have produced contradictory results. No evidence of absorption of free quercetin by the human gut has been found. Citrus fruits contain a wide variety of flavonoids. Any mutagenic activity of flavonols is probably affected by the presence of other flavonoids. Flavonol apparently present minimal risk in human diets. (46 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

33. EFFECTS OF 5-METHYLNICOTINAMIDE ON MOUSE L1210 CELLS EXPOSED TO N-METHYL-N-NITROSOUREA: MUTATION INDUCTION, FORMATION AND REMOVAL OF METHYLATION PRODUCTS IN DNA, AND UNSCHEDULED DNA SYNTHESIS.

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Carcinogenesis; 2(10):1013-1017 1981

Alkylation of L1210 DNA by N-methyl-N-nitrosourea (MNU) was measured, and the effects of 5'-methylnicotinamide (5MeN) on removal of methylated purines, on unscheduled DNA synthesis, and on induction of 6-thioguanine (6TG)-resistant mutants were examined. The loss of colony-forming ability of L1210 cells caused by MNU was potentiated 2.8-fold in the presence of 1 milliM 5MeN. 5MeN reduced the frequency of 6TG-resistant mutants induced by MNU: In two experiments, the induced mutation frequencies of cells not treated with 5MeN were 15.6 and 12.1 mutants per 10(4) surviving cells per milliM MNU compared with 7 mutants per 10(4) survivors per milliM MNU for mutations expressed and selected in the presence of 5MeN. 7-Methylguanine removal from DNA by MNU was unaffected by 5MeN, whereas O6-methylguanine (O6-MeG) was removed from 5MeN-treated cells at a significantly higher rate (half-life 28 hr) than from untreated cells (half-life 46 hr). 5MeN had no effect on inhibition of normal replicative DNA synthesis by 0.2 milliM hydroxyurea, whereas it stimulated unscheduled DNA synthesis under similar conditions. The observation that 5MeN reduces the frequency of 6TG-resistant mutants induced by MNU and enhances the rate of O6-MeG removal is consistent with this being a promutagenic lesion in L1210 cells. (48 Refs)

34. TISSUE-DEPENDENT ENZYME-MEDIATED REPAIR OR REMOVAL OF O-ETHYL PYRIMIDINES AND ET HYL PURINES IN CARCINOGEN-TREATED RATS.

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Carcinogenesis; 2(10):1069-1073 1981

Ten-day-old BD IX rats were injected with radiolabeled N-ethyl-N-nitrosourea (EtNU: 69.4 ug/kg, ip), and the sites and proportions of ethyl products, as well as their removal and repair, in DNA from various tissues was examined. One hr after carcinogen injection, DNA of brain, liver, and other pooled organs (spleen, lung, thymus, muscle, and intestine) showed similar proportions of the derivatives quantitated (O6-ethyl [Et] guanine [G], 7EtG, 3-Et adenine [A], O2-Et thymine [T], O4-EtT, O2-Et cytosine [C], and ethylphosphotriesters). During the 75 hr after carcinogen administration, most ethylated bases were poorly removed (or, in the case of O4-EtT, not at all) from DNA in the brain (the target tissue of EtNU carcinogenicity), and from DNA in the tissue pool. Removal from the brain appeared to cease after 25-50 hr. Kinetics of O6-EtG removal in brain and in the tissue pool were similar, except that there was a rapidly exhausted early and partial repair capability in brain. O-alkyl products were removed from the liver at progressively increasing rates over the entire 75-hr period. The accelerated loss of O2-EtT, O4-EtT, and O2-EtC may have been due either to an increase in hepatic protein synthesis as a result of recovery from EtNU-induced inhibition or to induction of an O-alkyl pyrimidine-specific enzyme. Triester levels remained almost unchanged in all tissues examined. However, the small decrease in the triester level observed in liver DNA suggested a half-life of greater than 1 wk. Any or all persistent promutagenic derivatives (O6-EtG, O2-EtT, O4-EtT, O2-EtC) may be important in initiation of carcinogenesis by somatic mutation. (45 Refs)

35. HOT SPOTS OF FRAMESHIFT MUTATIONS INDUCED BY THE ULTIMATE CARCINOGEN N-ACETOXY-N-2-ACETYLAMINOFLUORENE.

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Nature; 294(5842):657-659 1981

An important step in carcinogenesis is thought to be the initial attack of the DNA molecule by a so-called ultimate carcinogen. More than 90% of the carcinogens tested have been found to be mutagens in bacterial systems. The covalent binding of the ultimate carcinogen to the DNA bases or phosphate groups creates a premutational lesion that in vivo is processed by the repair, replication and recombination enzymes, and eventually may be converted into a mutation. Being interested in the way that an initial premutational event is converted into a stable heritable mutation, we have sequenced stable mutations in a gene that has formed covalent adducts in vitro with N-acetoxy-N-2-acetylaminofluorene (N-AcO-AAF, a m odel for the ultimate metabolite of the rat liver carcinogen 2-acetylaminofluorene AAF). We show here that the mutations are mainly frameshifts involving G-C base pairs, and that certain base pairs (hotspots) are affected at relatively high frequencies. These results fit a model in which N-AcO-AAF-modified guanine acts as a non-coding base that during replication results in deletion of the modified residue. (Author abstract) (23 Refs)

36. IN VITRO REACTION OF THE CARCINOGENIC DERIVATIVE N-ACETOXY-7-ETHYL-N-2-ACETYLAMINOFLUORENE WITH DNA. A SPECTROSCOPIC STUDY.

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Carcinogenesis; 2(10):1019-1025 1981

Reaction in vitro of DNA with N-acetoxy-7-ethyl-N-acetylaminofluorene (N-AcO-EtAAF) was compared with N-acetoxy-N-acetyl-2-aminofluorene (NAcO-AAF). Introduction of an ethyl group at position 7 of the fluorene ring induces an increase of reaction of this (model) metabolite of the carcinogen 2-acetoxy-2-aminofluorene (2-AAF) toward DNA and its constituents. UV absorption and circular dichroism spectroscopic methods were used to characterize the DNA reacted with N-AcO-EtAAF (DNA-EtAAF). Results indicate some conformational similarities between native DNA-EtAAF and DNA-AAF such as the presence of destabilized regions around the bound carcinogen and of stacking interactions between these residues and the adjacent nucleotides. Important differences appear to exist between adducts or modified sequences in native as compared to denatured DNA (contrary to DNA-AAF and DNA bearing covalently bound 2-aminofluorene). (19 Refs)

37. MODULATION OF THE COVALENT BINDING OF ARYL HYDROCARBON METABOLITES TO DNA IN VITRO AFTER TREATMENT OF RATS AND MICE WITH TRANS-STILBENE OXIDE.

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Carcinogenesis; 2(10):1049-1056 1981

Effects of trans-stilbene oxide (TSO) on in vitro microsome-mediated binding of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) to purified DNA were investigated. Chromatograms of enzyme digests of DNA obtained from incubation of labeled BP metabolites with hepatic microsomes from TSO-treated Sprague-Dawley rats showed a decrease in peak H (nucleoside-bound 9-hydroxy-BP-4,5-oxide) without any significant modification of peaks E (nucleoside-bound syn- and anti-BP-7,8-diol-9,10-epoxide) or G (nucleoside-bound BP-4,5-oxide). In vitro addition of the epoxide hydrolase inhibitor 1,1,1-trichloropropene 2,3-oxide (TCPO) produced 2.8-and 3.2-fold increases, respectively, in peaks G and H in microsomes from TSO-treated rats compared with those from controls. BP-metabolite-deoxyribonucle oside profiles obtained with microsomes from rats treated with BP (40 mg/kg) alone showed considerable covalent binding of BP-7,8-diol-9,10-epoxide and 9-hydroxy-BP-4,5-oxide; treatment with both BP and TSO (3 x 400 mg/kg) decreased binding to 45% and 25%, respectively. Microsomes from TSO-treated Swiss mice showed levels of BP-4,5-oxide and 9-hydroxy-BP-4,5-oxide binding that were 1.6-and 1.4-fold, respectively, greater than levels in microsomes from controls. The heights of peaks E, G, and H for C57BL/6 mice treated with TSO and BP were 53%, 60%, and 69% of the values obtained for mice treated with BP alone. After incubation of DNA with 3H-DMBA and BP- or TSO plus BP-treated rat liver microsomes, dual induction by BP and TSO was found to decrease DMBA metabolite binding to DNA, compared with induction by BP alone. The studies demonstrated the ability of TSO to increase the rate of oxidation at the K-region, due to induction of specific monooxygenases, and its ability to increase the rate of deactivation of epoxide intermediates by inducing microsomal epoxide hydrolase activity. The effects of TSO were similar for both substrates examined. (29 Refs)

38. METABOLISM OF 1-NITROPYRENE AND FORMATION OF DNA ADDUCTS IN SALMONELLA TYPHIMURIUM.

Messier F, Lu C, Andrews P, McCarry BE, Quilliam MA, McCalla DR
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Carcinogenesis; 2(10):1007-1011 1981

1-Nitropyrene was slowly reduced by intact cells of Salmonella typhimurium to 1-aminopyrine and N-acetyl-1-aminopyrene, as well as six minor metabolites. When tritiated nitropyrene was metabolized, some radioactivity was bound to DNA, with a time course similar to that for reduction of 1-nitropyrene. Max binding levels were of the order of one molecule of nitropyrene per 10(6) nucleotides in DNA. Results of DNA-binding experiments with nitroreductase-deficient strain TA100 F50 suggested that reductase activity present in TA100 (wild-type for nitroreductase) but absent from the F50 mutant is involved in the reductive 'activation' of 1-nitropyrene. Upon enzymatic hydrolysis of DNA, radioactivity appeared in low mol wt material, much of which eluted before the normal nucleosides. This material most likely represented an adduct or adducts formed between nitropyrene metabolites and nucleosides in DNA. Results with a uvr+ strain in this study, as well as results of previous studies, suggested that these adducts are subject to removal in strains proficient in excision repair. (18 Refs)

39. ALKYLATION OF N2 IN DEOXYGUANOSINE BY DEHYDRORETRONECINE, A CARCINOGENIC METABOLITE OF THE PYRROLIZIDINE ALKALOID MONOCROTALINE.

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Cancer Res; 42(1):8-14 1982

Dehydroretronecine, an antimitotic and carcinogenic agent, reacted with the deoxyguanosine at pH 7.4 in vitro to yield in nearly equal quantities two major adducts, which were isolated by thin-layer and high-pressure liquid chromatography. The adducts were stable at pH 8.7 and 30 C for at least 24 hr, showed pKas at acidic and alkaline pHs, reacted with 4-(p-nitrobenzyl)-pyridine, had a nonexchangeable guan-8-yl proton, and contained equimolar quantities of the pyrrole and nucleotide moieties. From the above data and comparison of proton magnetic resonance spectra of dehydroretronecine, deoxyguanosine, and the adducts, both products were identified as derivatives with a bond between C-7 of dehydrosupinidine and N2 of deoxyguanosine. Mass spectral fragmentation patterns and infrared and UV absorbance spectra were also consistent with N2 substitution. Circular dichroism spectra established the identities of each of the adducts as 7-(deoxyguanosin-N2-yl)dehydrosupinidine; they are enantiomeric at C-7. These results demonstrate that the reactive electrophile derived from protonated dehydroretronecine readily alkylates the N2 position of deoxyguanosine at C-7 in an SN1 reaction to yield a racemic mixture of products. (Author abstract) (34 Refs)

40. THE DISTRIBUTION OF BENZO(A)PYRENE DNA ADDUCTS IN MAMMALIAN CHROMATIN.

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Nucleic Acids Res; 9(21):5533-5552 1981

This paper describes the distribution of DNA-lesions generated by the potent carcinogen benzo(a)pyrene (BP) or its ultimate metabolic derivative 7alpha,8beta,di-hydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDE) within mammalian chromatin using the enzymic probe micrococcal nuclease. We have shown that the progress of the nuclease on naked DNA is unaffected by the presence of the hydrocarbon lesion at moderate extents of digestion. Digestion of nuclei isolated from murine erythroleukemic cells immediately following BPDE treatment, and analysis of micrococcal nuclease resistant DNA by TCA precipitation, hydroxyapatite chromatography and gel electrophoresis demonstrates a non-random distribution of lesions. Approx 3x more binding occurs on the linker DNA regions between nucleosome cores than on the nucleosome core DNA itself. A similar result was obtained with BPDE treated primary mouse embryo cells; however nuclei isolated from these cells after prolonged treatment with BP (to allow metabolic activation) showed no such preferential binding. Post-treatment incubation of PBDE-treated cells shows that this difference can be accounted for by the loss of preferential localization with time. (Author abstract) (33 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

41. DEVELOPMENTAL ONSET OF MIXED-FUNCTION OXIDASE ACTIVITY IN PREIMPLANTATION MOUSE EMBRYOS.

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Proc Natl Acad Sci USA; 78(11,part2):6991-6995 1981

Two-cell embryos, obtained from the C57BL/6N and DBA/2N strains, were cultured in media that supported in vitro differentiation and that contained [3H]benzo[a]pyrene. High-pressure liquid chromatography of the activated intermediates formed during in vitro early embryonic development indicated that the onset of polynuclear aromatic hydrocarbon activation coincided with blastocyst formation. Comparison of individual oxygenated intermediates metabolically formed from embryos genetically 'responsive' or 'nonresponsive' to aromatic hydrocarbons revealed significant quantitative differences in the production of dihydrodiol, quinone, and phenolic derivatives. In addition to exhibiting basal mixed-function oxidase activity, blastocysts were also responsive to enzymatic induction when exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. The presence of operative metabolite-detoxifying pathways was also assayed. Enzymatic treatment of water-soluble metabolites with beta-glucuronidase or arylsulfatase revealed that neither glucuronic acid conjugates nor sulfate ester derivatives were present. These data, therefore, provide direct evidence that late preimplantation mouse embryos (day 3 1/2 of gestation) are similar to later developmental stages in having the enzymatic capability for xenobiotic activation and enzyme induction but are dissimilar with respect to their detoxification mechanism(s). Moreover, the ability of preimplantation embryos to activate directly polynuclear aromatic hydrocarbon to bioreactive intermediates may be of importance in assessing the ontological susceptibility of the developing embryo to carcinogenic or teratogenic chemicals. (Author abstract) (27 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

42. CORRELATIONS AMONG THE CHANGES IN HEPATIC MICROSOMAL COMPONENTS AFTER INTOXICATION WITH ALKYL HALIDES AND OTHER HEPATOTOXINS.

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Dept. Pathology, Univ. California Sch. Medicine, San Francisco, CA, 94143
Mol Pharmacol; 20(3):685-693 1981

Male Sprague-Dawley rats were treated with 13 alkyl halides (carbon tetrachloride, bromotrichloromethane, chloroform, bromoform, dichloromethane, dibromomethane, 1,2-dichloroethane, 1,2-dibromomethane, 1-bromo-2-chloroethane, 1,1,2-trichloroethane, 1,2,3-trichloropropane, 1,2-dibromo-3-chloropropane, and 1,2-epoxy-3-chloropropane) and 4 other hepatotoxins (dimethylnitrosamine (DMN), thioacetamide, ethionine, and cadmium acetate) and the content of several microsomal components was assayed. O nly two of the treatments, CCl4 and CBrCl3, resulted in measurable peroxidation of microsomal lipids. These compounds also caused significant decreases in microsomal protein. phospholipid, cytochrome P-450, cytochrome b5, NADPH cytochrome c reductase, stearic acid, and arachidonic acid within 18 hr of treatment. The other alkyl halides tested have higher halocarbon bond-dissociation energies and would be less likely to be metabolized via homolytic cleavage of the halocarbon bonds, which is associated with lipid peroxidation. DMN also had widespread effects on microsomal components but caused no peroxidation of microsomal fatty acids or loss of phospholipid, whereas a significantly lower amount of RNA was recovered from the microsomes. Microsomal responses to the majority of the compounds showed two major similarities: a significant decrease in cytochrome P-450 and a shift in the composition of microsomal fatty acid, primarily characterized by a decrease in arachidonic acid and an increase in linoleic acid. (35 Refs)

43. THE EFFECT OF 3-METHYLCHOLANTHRENE AND 3-METHYLCHOLANTHRENE PLUS PIRACETAM ON THE GAMMA-AMINOBUTYRIC ACID (GABA) CONTENT OF SEVERAL CEREBRAL REGIONS.

von Metzler A, Nitsch C
Max-Planck-Institut fur Hirnforschung, D-6000 Frankfurt a. M., W. Germany
J Cancer Res Clin Oncol; 101(3):339-343 1981

The effects of piracetam (PA) on elevation of gamma-aminobutyric acid (GABA) in cerebral regions of female Wistar rats by 3-methylcholanthrene (3-MC) were studied. Groups of rats were treated variously with PA (100 mg/kg body wt/administration, delivered by stomach tube), 3-MC (6 mg/kg body wt/administration, sc), or combinations of both. Total doses and timing of treatments varied. Treatment with 3-MC produced a rapid elevation of GABA in the hypothalamus and a more delayed elevation in the hippocampus. Walker's carcinoma also produced elevated GABA in these regions. PA alone did not affect GABA levels. Short-term PA treatment did not reduce GABA levels elevated by 3-MC, but chronic PA treatment reduced GABA to the lowest levels of any of the experimental conditions. PA was specific for the CNS and did not affect peripheral areas. Amino oxyacetic acid, which inhibits GABA-transaminase, caused elevated GABA levels in the brain and apparently increased tumor rates in rats treated with 3-MC. Although only 3-MC and PA were tested, results suggest a relationship between CNS effects and peripheral carcinogenesis. (13 Refs) (In GER)

44. EXCESSIVE ACCUMULATION OF AUTOFLUORESCENT LIPOFUSCIN IN THE LIVER DURING HEPATOCARCINOGENESIS BY METHYL CLOFENAPATE AND OTHER HYPOLIPIDEMIC PEROXISOME PROLIFERATORS.

Reddy JK, Lalwani ND, Reddy MK, Qureshi SA
Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611
Cancer Res; 42(1):259-266 1982

Several hypolipidemic drugs and certain industrial plasticizers induce proliferation of peroxisomes and enhance the activities of peroxisome-associated enzymes in the livers of rodents. Evidence now suggests that potent hepatic peroxisome proliferators as a class are carcinogenic, although they do not appear to be mutagenic in the Salmonella-microsome assay system. We now report that long-term administration of methyl-2-[4-(p-chlorophenyl)phenoxy]-2 methylpropionate, a potent hepatic peroxisome proliferator, at a dietary concentra-

tion of 0.1% (w/w), induced hepatocellular carcinomas in 14 of 14 male F344 rats between 65 and 75 wk. The tumor cells contained several peroxisomes. Consistent with this observation was the finding of increased levels of carnitine acetyltransferase, heat-labile peroxisomal enoyl coenzyme hydratase, and peroxisomal beta-oxidation system in the tumors. As expected, methyl clofenapate was not mutagenic in the Salmonella-microsome assay using Salmonella typhimurium strains TA98 and TA100. Abundant accumulation of autofluorescent lipofuscin in the nontumorous portions of liver in rats bearing methyl-2-[4-(p-chlorophenyl)phenoxy]-2-methylpropionate induced hepatocellular carcinomas was observed. The examination in this study of livers of rats bearing hepatocellular carcinomas induced previously by five other hypolipidemic peroxisome proliferators provided retrospective evidence for increased accumulation of autofluorescent pigment in the liver cells. It is suggested that accumulation of lipofuscin in the livers of rats fed peroxisome proliferators serves as evidence for the increased production of biologically damaging free radicals as a result of H2O2 generated by sustained proliferation of peroxisomes. the hypothesis that persistent proliferation of peroxisomes and increase in peroxisomal beta-oxidation system initiates the neoplastic transformation of liver cells by increasing the intracellular production of DNA-damaging H2O2 and other reactive oxygen intermediates (OH-, O2-, 1O2) remains to be tested. (Author abstract) (49 Refs)

45. RAPID INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE-RICH INTRAEPITHELIAL CLONES IN 7,12-DIMETHYLBENZ(A)ANTHRACENE-TREATED HAMSTER BUCCAL POUCH.

Solt DB, Shklar G

Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA, 02115

Cancer Res; 42(1):285-291 1982

Individual gamma-glutamyl transpeptidase (GGT)-stained cells and cell doublets were rapidly induced in the epithelium of hamster buccal pouch treated with biweekly topical applications of 0.5% 7,12-dimethylbenz(a)anthracene (DMBA) in mineral oil. The cells were detected histochemically in whole mounts of pouch epithelium harvested as early as 3 days after the first application of this carcinogen. During 3 consecutive wk of DMBA treatment, progressively larger GGT-stained epithelial ce ll populations (plaques) up to 0.5 mm in diameter were encountered. Similar GGT-stained lesions were not detected in whole mounts of untreated epithelium and were rarely seen in GGT-stained whole mounts prepared from mineral oil-treated pouch epithelium. In an experiment designed to assess the stability of the GGT-staining pattern, very few plaques could be detected 12 wk after a 3-wk regimen of six DMBA applications. However, data are presented suggesting that a brief series of three DMBA applications reinduced GGT histochemical activity in occult intraepithelial plaques, which had lost enzyme activity but had persisted over an 11-wk treatment-free interval. The clonal nature of the GGT-stained plaques and their apparent ability to persist in an occult form for several wk or mo lend further support to the hypothesis that these carcinogen-altered cell populations may be potential precursors for the development of squamous epithelial neoplasia. (Author abstract) (40 Refs)

46. GAMMA-GLUTAMYLTRANSPEPTIDASE: A TUMOR CELL MARKER WITH A PHARMACOLOGIC FUNCTION.

Vanderlaan M, Phares W

Biomedical Sciences Div., Lawrence Livermore Natl. Lab., P.O. Box 5507, Livermore, CA, 94550

Histochem J; 13(5):865-877 1981

The histochemical distribution of gamma-glutamyltranspeptidase (GGTP) in rat and human tissues is reviewed, and the changes observed during embryogenesis and carcinogenesis are discussed. The pattern of GGTP distribution is similar in both species, with activity in adults found primarily in the proximal tubules of the kidney, the secretory follicle cells of the pancreas, and the villous cells of th jejunum. There is only minimal activity in intestinal crypt cells, but considerable in mature villus cells. Mammary gland, bile duct cells in adult liver, endothelial cells of brain capillaries, follicle sheath cells in actively growing hairs, and lymphocytes also have associated GGTP activity. Higher activity is seen in both embryonal and cancerous tissues. Soon after initial exposure to carcinogens, islands of presumably preneoplastic cells form in the liver, and are characterized by very high GGTP activity. The majority of hyperplastic nodules and carcinomas that eventually develop also have increased GGTP activity. This induction of increased activity persists long after carcinogen exposure. The possible metabolic significance of GGTP is discussed. (63 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

47. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

Ioannides C, Delaforge M, Parke DV

Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England

Food Cosmet Toxicol; 19(5):657-666 1981

This review of safrole metabolism is aimed at elucidating the importance of the allyl moiety and the methylenedioxy group in the mechanism of carcinogenesis. It includes studies concerning safrole carcinogenicity, interactions of safrole with cytochrome P-450, inhibition of mixed-function oxidase activity by safrole, ligand complex formation with cytochromes P-450 and P-448, and hemoprotein formation by safrole and isosafrole. Ligand complexing and covalent binding of reactive intermediates with the heme and protein moieties, respectively, of cytochrome P-450, may be fundamental to the mechanism of safrole carcinogenesis. Structural and functional properties of the cytochrome are substantially changed by this binding, which, since ribosomes are attached to the endoplasmic reticulum at cytochrome P-450, may be associated with loss of ribosomes known to occur following treatment with safrole or other carcinogens. Chemical carcinogenesis is associated with increases in hepatic cytochrome P-448 and simultaneous loss of cytochrome P-450 activity and could, through loss of ribosomes, result in impairment of glycoprotein synthesis and thus contribute to malignant transformation by epigenetic mechanism. Therefore, of the two functional groups of safrole, the allyl group has been shown to be associated with mutagenicity, and the methylenedioxy moiety to be associated with changes to cytochrome P-450 and possibly with epigenetic aspects of carcinogenicity. (84 Refs)

48. CHEMICAL CARCINOGENESIS.

Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

Fundamental concepts related to the causation, prevention, and therapy of cancer in humans are reviewed, with emphasis on mechanistic aspects. Topics include cancer as a chronic multistage process, initiators and initiation (initiators, activation and metabolism of procarcinogens, possible molecular targets for ultimate carcinogens, DNA repair, carcinogen metabolism in human tissues, initiation), promoters and promotion (promoters, promotion, subsequent steps - progression and transfection, diet and carcinogenesis, chemotherapy and carcinogenesis), and new bioassays for carcinogens and promoters. Illustrations of (1) the current view on activation of benzo(a)pyrene to benzo(a)pyrene 7,8 dihydrodiol,9,10 epoxide, (2) sites of interactions of activated forms of carcinogens with the four DNA bases, and (3) steps in the initiation of carcinogenesis with chemicals are presented. Later phases of chemical carcinogenesis, ie post-initiation phenomena including promotion, and the relative quantitative importance of exogenous or endogenous chemical carcinogens in patients with cancer not related to smoking are not sufficiently understood. (118 Refs)

49. TUMORIGENICITY OF BAY-REGION DIOL-EPOXIDES AND OTHER BENZO-RING DERIVATIVES OF DIBENZO(A,H)PYRENE AND DIBENZO(A,I)PYRENE ON MOUSE SKIN AND IN NEWBORN MICE.

Chang RL, Levin W, Wood AW, Lehr RE, Kumar S, Yagi H, Jerina DM, Conney AH
Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche, Inc., Nutley, NJ, 07110
Cancer Res; 42(1):25-29 1982

Dibenzo(a,h)pyrene [DB(a,h)P], dibenzo(a,i)pyrene [DB(a,i)P], and seven of their benzo-ring derivatives were tested for tumorigenic activity on mouse skin and in newborn mice. In the tumor studies on mouse skin, a single topical application of 50, 200, or 600 nmol of compound was followed 7 days later by twice-weekly applications of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate for 16 or 24 wk. With the exception of 2,10-difluorodibenzo(a,i)pyrene, all of the compounds had significant tumor-initiating activity at all doses tested. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene, the metabolic precursors of bay-region diol-epoxides, had tumor-initiating activity that was equivalent to their parent hydrocarbons. Saturation of the double bond in the benzo-ring of these dihydrodiols resulted in the formation of tetrahydrodiols whose tumor-initiating activity was not significantly different from that observed with the corresponding dihydrodiols at the 50-nmol dose. The bay-region diol-epoxides of DB(a,h)P and DB(a,i)P, in which the benzylic hydroxyl group and the oxirane oxygen are trans (Isomer 2), induced significantly fewer tumors per mouse than did their dihydrodiol and parent hydrocarbon precursors. In the tumorigenicity study in newborn mice, a total dose of 87.5 nmol of the hydrocarbon divided into three ip injections was administered on the 1st, 8th, and 15th day of life, and tumorigenic activity was determined when the mice were 49 to 54 wk old. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene induced three- to eight-fold more pulmonary tumors per mouse and four- to five-fold more hepatic tumors per male mouse than the respective parent hydrocarbons. The corresponding tetrahydrodiols had no more than one-eighth of the pulmonary tumorigenic activity of the corresponding dihydrodiol. The bay-region diol-epoxide (Isomer 2) of DB(a,h)P had tumorigenic activity equal to the parent hydrocarbon but significantly less than its dihydrodiol precursor. The bay-region diol-epoxide (Isomer2) of DB(a,i)P was highly toxic, and only 19% of the mice survived to termination of the study. This diol-epoxide had significantly less tumorigenic activity towards the lung than did either its dihydrodiol precursor or the parent hydrocarbon. Notably, 20% of the surviving mice treated with the diol-epoxide of DB(a,i)P had leukemia at the termination of the study. 2,10-Difluorodibenzo(a,i)pyrene had no tumorigenic activity in newborn mice at the single dose tested. These results are discussed in relationship to the bay-region theory of polycyclic aromatic hydrocarbon carcinogenicity. (Author abstract) (27 Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
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Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
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5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
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Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
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6. NUTRITION AND CANCER: A REVIEW.
Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
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7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

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8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIOPATHOGENESIS OF ACUTE LEUKAEMIA.
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Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
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10. CANCER FAMILY SYNDROME.
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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

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Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

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Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

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14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
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15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
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16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
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Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
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18. VIRUS PAPILLOMAS IN HUMANS.
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Activation and Metabolism of Carcinogens

SERIES CK08 No. 82/05 MAY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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METABOLIC ACTIVATION OF CARCINOGENS

1. POLYCYCLIC HYDROCARBON METABOLISM: A PLETHORA OF PHENOMENA.

Estabrook RW, Saeki Y, Chacos N, Capdevila J, Prough RA
Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
Adv Enzyme Regul; 19:3-17 1981

Studies of benzo(a)pyrene metabolism by liver microsomes have revealed a complex pattern of products formed. The distribution of products generated depends on the types of cytochromes P-450 present and the mechanism of oxidation reactions catalyzed. It is proposed that cytochrome P-450 may function to catalyze the oxidation of benzo(a)pyrene not only by a NADPH-dependent monooxygenation type reaction, but also concomitantly by a peroxidatic type reaction. In particular, attention is directed to the role of the latter type of reaction for the formation of benzo(a)pyrene quinones. The pathways for the metabolic generation of quinones, as well as the reactivity of hydroquinones with oxygen, provide additional pathways for the formation of highly reactive, toxic products which may contribute to the alterations of cellular characteristics that result in either tumor growth or cell death. (Author abstract) (43 Refs)

2. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Aerosp Med Biol; (224):173 1981

An environmental agent, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than in the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

3. COMPARATIVE METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND SEVERAL FLUORINATED ANALOGUES IN SYRIAN HAMSTER EMBRYO CELL CULTURE AND IN SPRAGUE-DAWLEY AND LONG-EVANS RATS IN VIVO.

Oravec CT
Ohio State University, Columbus, OH
Diss Abstr Int [B]; 42(5):1844-B 1981

The metabolities resulting from the rat liver microsomal oxidation of 7-12,dimethylbenz(a)anthracene (DMBA) and its fluoro analogs were compared to the metabolites from treatment of Syrian hamster embryo (SHE) cell cultures with [3H]DMBA, [3H]2F-DMBA, [14C]5F-DMBA and [3H]11F-DMBA, SHE cells in culture were exposed to each of the above DMBA analogs up to 24 hr and the metabolites both within and outside the cell (in the media) were isolated and analyzed by high pressure liquid chromatography and fluorescence spectroscopy. Metabolites were also separated into their free and conjugated components by alumina chromatography and treated with either B-glucuronidase or sulfatase enzymes to identify their conjugated components. These studies were subsequently compared to the in vivo analysis of DMBA and 2F-DMBA in Sprague-Daw ley and Long-Evans fifty day old, female rats. These two strains were chosen because of their sensitivity and resistance, respectively, to assult by DMBA and the subsequent development of mammary tumors. The DMBA and 2F-DMBA metabolites isolated from the urine of these rats were analyzed using similar techniques as those described above for the SHE cell metabolism. Several differences between the two species were noted. (no Refs)

4. CYTOTOXIC EFFECTS AND METABOLISM OF BENZO[A]PYRENE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN DUODENAL AND ILEAL EPITHELIAL CELL CULTURES.

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Gastrointestinal Unit, Massachusetts General Hosp., Boston, MA, 02114
JNCI; 67(6):1353-1362 1981

Two epithelial cell lines have been established from the duodenum (IEC-17) and the ileum (IEC-18) of outbred germ-free Crl:CD(SD)GN rats. They have a very similar morphology and ultrastructure, a normal rat diploid karyotype, comparable growth rates, and a similar set of surface antigens as detected with monoclonal antibodies specific for intestinal epithelial cell surface proteins in vivo. Both cell lines do not grow in soft agar and when injected into syngeneic animals do not form tumors. The toxic effects of benzo[a]pyrene (BP) and 7,12-dimethylbenz[a]anthracene (DMBA) were studied in these two cell lines. The IEC-18 cells were found to be much more sensitive to both chemicals than the IEC-17 cells. In particular, at concentrations greater than 1 ug/ml, DMBA completely and irreversibly inhibited cell proliferation in the IEC-18 cells, whereas it produced a less marked and reversible inhibition in the IEC-17 cells. The metabolism of BP and DMBA to water-soluble products was studied; BP was apparently metabolized at similar rates in the two cell lines, whereas a striking difference was observed with DMBA, which was metabolized at a rate 10-15x greater in the IEC-18 cells than that in the IEC-17 cells. These results suggest that cultured cell lines derived from different portions of the intestinal tract have similar properties in vitro, but they may have very different responses to chemical carcinogens. (Author abstract) (34 Refs)

5. ELECTROSTATIC MOLECULAR POTENTIAL CONTOUR MAPS GENERATED FROM AB INITIO MODPOT/VRDDO/MERGE WAVE FUNCTIONS OF CARCINOGENIC 3-METHYLCHOLANTHRENE AND ITS METABOLITES.

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Int J Quantum Chem; 20(5):1083-1095 1981

Electrostatic molecular potential contour maps were calculated for 3-methylcholanthrene (3-MCA), its metabolites 3-MCA 7,8-oxide and 3-MCA 9,10 oxide, and the stereoisomers 3-MCA 9,10-dihydrodiol-7,8-epoxide A beta beta beta and 3-MCA 9,10-dihydrodiol-7,8-epoxide A alpha beta alpha. Results show that the electrostatic molecular potential contour maps may be used to indicate favored positions of at tack for electro-

philic species, such as 'electrophilic' oxygen to form an epoxide as well as for positive ion attack; maps for 3-MCA indicate the favored site for attack and pathways. The maps around 3-MCA 9,10-oxide and 3-MCA 9,10-dihydrodiol-7,8-epoxide indicate the directional preferences for proton assisted epoxide ring opening. By convention, atoms below the plane of the remaining rings of 3-MCA are shown on the maps as dotted, while atoms above the plane are shown as dashed. Maps around the 3-MCA dihydrodiols indicate that for certain stereoisomers the 'electrophilic' oxygen will prefer to attack from below, but for other isomers the oxygen will attack from above. Mapping provides insight into stereochemical preference for formation of different 3-MCA 9,10-dihydrodiol-7,8-epoxides. (20 Refs)

6. PATHOGENESIS OF LUNG TUMORS INDUCED BY N-NITROSOHEPTAMETHYLENEIMINE IN F344 RATS.

Reznik-Schuller HM, Gregg M
Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
Virchows Arch [Pathol Anat]; 393(3):333-343 1981

Male F344 rats were given 3 mg N-nitrosoheptamethyleneimine (NHMI) per 100 g in olive oil by gavage twice a wk for a max of 20 wk. They were killed at predetermined intervals after the start of treatment and the sequential development of NHMI-induced squamous carcinomas in the lungs was followed by light and electron microscopy. Hypertrophy of the endoplasmic reticulum in mucous and Clara cells seen in an initial study suggested that these cells were involved in metabolic activation of the nitrosamine. Basal cells were identified as the cell type that later responded by proliferation, hyperplasia, and squamous metaplasia. Only in the bronchioles, where basal cells are not found in the healthy rat, did these lesions progress further to form squamous cell carcinomas. (Author abstract) (13 Refs)

7. METABOLIC FATE OF ASYMMETRIC N,N-DIALKYLNITROSAMINES HAVING A BUTYL GROUP IN THE RAT.

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Tokyo Biochemical Res. Inst., Takada 3-14-8, Toshima-ku, Tokyo 171, Japan
Gan; 72(6):910-920 1981

The metabolic fate of N-alkyl-N-butylnitrosamines (alkyl=ethyl, propyl, and pentyl), which induce tumors in the liver and esophagus but do not induce bladder tumors, was investigated in the rat, in order to elucidate any possible correlation between metabolism and the noncarcinogenicity to the urinary bladder of these N-nitrosamines. They were extensively metabolized in the rat, no unchanged compounds being found in the urine. The metabolic pattern of these N-nitrosamines having a butyl chain was essentially similar to that of N,N-dibutylnitrosamine, which induces tumors in the bladder as well as in the liver and esophagus. They were mainly metabolized via omega-oxidation followed by beta-oxidation and/or (omega-1)-oxidation of either of the two alkyl chains. Thus the N-alkyl-N-(3-carboxypropyl)nitrosamine and/or the N-alkyl-N-(2-carboxyethyl)nitrosamine were identified as the principal urinary metabolites. Possible important factors concerned with the induction of bladder tumors by N,N-dialkylnitrosamines are discussed from the metabolic point of view. (Author abstract) (21 Refs)

8. A CHROMATOGRAPHIC TECHNIQUE FOR ANALYSIS OF OXIDIZED METABOLITES AND APPLICATION TO CARCINOGENIC N-HYDROXYARYLAMINES IN URINE.

Frederick CB, Mays JB, Kadlubar FF
Div. Carcinogenesis Res., Natl. Center for Health and Human Services, Jefferson, AR,
Anal Biochem; 118(1):120-125 1981

A new chromatographic detection method for N-oxidized metabolites has been developed based on the reaction of compounds with an Fe+++-bathophenanthroline disulfonic reagent in a postcolumn reactor. The method is applicable to N-hydroxyarylamines, aryldiamines, phenylenediamines, and ascorbic acid. It has been applied to the analysis of N-oxidized metabolites in rhesus monkey urine after the animals were dosed with the bladder carcinogen 4-aminobiphenyl or its metabolite N-hydroxy-4-aminobiphenyl. These compounds are oxidized to N-hydroxyarylamines in the liver, conjugated with glucuronide, and excreted in the urine. The N-glucuronides are shown to undergo acidic hydrolysis in the urine to yield the free N-hydroxyarylamine, an ultimate carcinogen responsible for induction of bladder tumors. In this study, the N-glucuronide of 2-naphthylamine was found to be excreted at a rate that was 6.8x that of the 1-naphthylamine isomer, a result consistent with the much higher carcinogenicity of 2-naphthylamine in a variety of species. (Author abstract) (15 Refs)

9. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

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Dept. Pharmacology, Coll. Pharmacy, Univ. of TX, 78712
Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of promutagens and procarcinogens to toxic intermediates and to study the mechanisms by which these chemicals produce cell death. This model was employed to investigate the cytotoxicity resulting from the biotransformation of cyclophosphamide (CP) to 4-hydroxy metabolites that nonspecifically alkylate cellular macromolecules, including proteins. The parenchymal cells were isolated by the collagenase perfusion technique and cultured for 24 hr before treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-2) M. Preliminary studies indicated minimal toxicity to cultures of parenchymal hepatocytes maintained in ornithine- and arginine-deficient medium. The addition of 3T3 cells caused overgrowth of fibroblasts in the same cultures. These fibroblasts then became the target of alkylating metabolites produced by the parenchymal cells. By 48 hr after CP administration, cell number and total protein were reduced by over 40%. The morphology of the cultures was altered specifically because of fibroblast destruction. The toxicity to the overlying fibroblasts was eliminated by adding SKF-525A, 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride, a specific inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reaction of the culture medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. The results provide both direct and indirect evidence for metabolism in cultured cells and suggest that the

can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

10. STUDIES ON THE MECHANISM OF METABOLIC ACTIVATION OF FTORAFUR (R,S-1-(TETRAHYDRO-2-FURANYL)-5-FLUOROURACIL) TO 5-FLUOROURACIL.

Au JL
University of California, San Francisco, CA
Diss Abstr Int [B]; 42(5):1903-B 1981

We have studied the metabolism, pharmacokinetics, enzyme systems responsible for the activation, and the extent of conversions of ftorafur (FT). We have developed high pressure liquid chromatographic assays and gas chromatographic assays to study the pharmacokinetics and metabolism of FT in animals and patients. The disposition of FT in rats, rabbits, and humans followed two compartment kinetics with mean beta phase half-lives of 5, 2, and 9 hr, respectively. Plasma concentrations of FU in FT-treated animals and patients were exceedingly low. Seven FT metabolites have been identified in plasma and urine samples of experimental animals and humans. A few metabolic activation pathways of FT to FU have been established. One of the major activation pathways of FT in rabbits and humans is mediated by the soluble enzymes in liver homogenates, and is not dependent on the hepatic microsomal cytochrome P-450 enzymes. Pharmacokinetic analysis of the plasma concentrations of FT and FU indicate that the conversion of FT to FU may also occur in target tissues, and the FU generated would be further metabolized without redistributing into the general circulation due to its rapid intracellular metabolism. This is consistent with the observed antitumor activity of FT in spite of the exceedingly low plasma concentrations of FU, and is further supported by the finding that the major metabolic activation pathway of FT to FU is mediated by soluble enzymes. (no Refs)

OTHER METABOLISM OF CARCINOGENS

11. CONJUGATION PATHWAYS IN HUMAN BRONCHIAL CARCINOMA CELL LINES.

Gibby EM, Mehta R, Ellison M, Cohen GM
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Biochem Pharmacol; 30(24):3333-3336 1981

Human bronchial carcinoma cell lines in monolayer cell culture were used to study the conjugation of 1-naphthol and 3-hydroxybenzo(a)pyrene, two phenolic substrates. Cell lines, able to metabolize 1-naphthol to glucuronic acid and sulfate ester conjugates, showed a predominance of glucuronidation. This is in sharp contrast to normal human peripheral lung which metabolizes these phenolic substrates predominantly to the sulfate ester conjugates. The bronchial tumor cell lines do not all have the same conjugation pattern and they differ in the metabolism of phenolic substrates when compared to normal peripheral lung. The cell lines generally show that sulfate ester conjugation was either reduced or absent. In some cases, dependent on the type of tumor the cell line was derived from, glucuronic acid conjugation was elevated. Initial sub-cellular studies with a poorly differentiated epidermoid cell line (Ben) demonstrated that this line had an active UDP-glucuronosyltransferase (Km 33 uM and Vmax 1.8 nmoles min-1.mg protein(-1)), using 1-naphthol as substrate. However, this cell line was unable to form significant amounts of sulfate ester conjugates, due to either low sulfotransferase activity, or an inability to generate adenosine 3'-phosphate 5'-sulfatophosphate (PAPS). (Author abstract) (20 Refs)

12. DISPOSITION OF THE FLAME RETARDANT, TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE, IN THE RAT.

Lynn RK, Wong K, Garvie-Gould C, Kennish JM
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Drug Metab Dispos; 9(5):434-441 1981

Distribution, metabolism, and excretion of tris(1,3-dichloro-2-propyl)phosphate (TDCP) were examined in male Sprague-Dawley rats. Five days after iv administration of 14C-TDCP, 54%, 22%, and 16% of the administered radiolabel was found in the urine, expired air, and feces, respectively; 4% was recovered in the body. TDCP was metabolized to bis(1,3-dichloro-2-propyl)phosphate (BDCP), which was the major urinary, fecal, and biliary metabolite. Other metabolites included 1,3-dichloro-2-propyl phosphate and 1,3-dichloro-2-propanol. TDCP was rapidly distributed out of plasma and into tissues. Less than 19% of administered TDCP was recovered as TDCP in the body 30 min after dosing. Rapid disappearance of TDCP was not due to excretion, as 82% of the administered radiolabel remained in the body and only traces (less than 0.1%) of the administered dose were found in the urine and feces as TDCP 30 min after dosing. Metabolism to BDCP was the major route of elimination of TDCP, whereas BDCP was eliminated primarily by excretion, with 63% of the administered phosphate (TDCP) recovered as BDCP in the urine and feces. 1,3-Dichloro-2-propan ol was mutagenic in Salmonella typhimurium TA100 without metabolic activation. TDCP was weakly mutagenic following activation with mouse phenobarbital-induced liver homogenates. Analysis of mutagenicity data on the basis of the number of revertants/umole demonstrated that TDCP was 3-20x more potent than 1,3-dichloro-2-propanol, suggesting that a metabolite other than the alcohol may be responsible for TDCP mutagenicity. Under the same conditions, BDCP and 1,3-dichloro-2-propyl phosphate were not mutagenic. (22 Refs)

MODIFICATION OF CARCINOGEN METABOLISM

13. STUDIES ON THE IN VITRO METABOLISM OF AFLATOXIN B1 AND G1 IN THE LIVER OF RATS FED AT VARIOUS LEVELS OF VITAMIN C.

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Biochem Pharmacol; 30(24):3317-3322 1981

Male and female weanling rats, divided into three groups, were maintained for 30, 60 and 90 days on an experimental diet without vitamin C. The drinking water containing or devoid of vitamin C was offered each day. The first group had no vitamin C; the second group or control had normal vitamin C and the third group had above-normal vitamin C in the water. Twenty-four hr after the last feeding, the animals were decapitated and the liver microsomes plus soluble fraction (9,000 g) were prepared. This preparation was used for O-demethylase and the hydroxylase assays of aflatoxins B1 and G1 (AFB1 and

AFG1). Results from O-demethylation in both control and experimental groups of both sexes, showed that O-demethylase activity is directly related to ascorbic acid content of the water. But the hydroxylase activity in male and female animals maintained on the same diet showed only slight differences. In the male, there was an increase with time of hydroxylase activity with AFB1 up to 60 days and a decrease at 90 days. Hydroxylation assay revealed that in the female, metabolism of AFB1 increased at 30 days but decreased at 60 and 90 days. (Author abstract) (29 Refs)

MUTAGENICITY OF ACTIVATED METABOLITES OF CARCINOGENS

14. THE INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY K-REGION EPOXIDES AND SOME DIHYDRODIOLS DERIVED FROM BENZ[A]ANTHRACENE, DIBENZ[A,C]ANTHRACENE AND DIBENZ[A,H]ANTHRACENE.

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Mutat Res; 84(2):389-398 1981

Benz[a]anthracene (BA), dibenz[a,c]anthracene (DB[a,c]A), dibenz[a,h]anthracene (DB[a,h]A), and some of their metabolites were studied for induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells. BA and 1,2; 5,6-; 8,9-; and 10,11-diols induced some SCE, but they were not as active as either benz[a]anthracene 5,6-oxide, which induced an approx 2-fold increase in SCE at 1 ug/ml, or trans-3,4-dihydro-3,4-dihydroyxbenz[a]anthracene. Despite the strong cytotoxicity of DB[a,c]A, it did not induce SCE. However, all DB[a,c]A metabolites tested (1,2-; 3,4-; and 10,11-dihydrodiols) induced SCE in a dose-dependent manner; trans-1,2-dihydro-1,2-dihydroxybenz[a,c]anthracene (4 ug/ml) induced a greater than 4-fold increase in SCE. DB[a,h]A was only weakly active. Trans-3,4-dihydro-3,4-dihydroxydibenz[a,h]anthracene was the most active DB[a,h]A metabolite, producing a greater than 3-fold increase in SCE at 2 ug/ml. Dibenz[a,h]anthracene 5,6-oxide actively induced SCE in a dose-dependent manner, whereas the 5,6-and 1,2-diols were almost inactive. K-region 5,6-epoxides derived from BA and DB[a,h]A were more active than the parent hydrocarbon in inducing SCE. Data suggest that when activated, the three polycyclic aromatic hydrocarbons studied can be metabolized to the ultimate carcinogen in CHO cells possessing some microsomal monooxygenase. (35 Refs)

15. MUTAGENICITY AND CYTOTOXICITY OF ETHYLENE OXIDE IN THE CHO/HGPRT SYSTEM.

Tan EL, Cumming RB, Hsie AW
Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830
Environ Mutagen; 3(6):683-686 1981

Cytotoxicity and mutagenicity of ethylene oxide (EO) in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) system were examined. EO was found to be a direct acting mutagen and cytotoxic agent. Mutation frequency showed a linear dose response; mutagenic activity of EO was 24.7 x 10(-6) mutants/clonable cell/millimole. Compared to halogenated ethanes such as ethylene dibromide, ethylene chlorobromide, and ethylene dichloride, EO is only less mutagenic than ethylene dibromide. S9 increased the cytotoxicity of ethylene chlorobromide and ethylene 5-25x and mutagenicity 4x; cytotoxicity of ethylene dibromide remained unchanged. (20 Refs)

16. MUTAGENICITY OF URINARY METABOLITES OF BENZIDINE AND BENZIDINE-BASED AZO DYES.

Tanaka K, Mii T, Marui S, Matsubara I, Igaki H
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Int Arch Occup Environ Health; 49(2):177-185 1981

Mutagenicity of urinary metabolites of benzidine and benzidine-based azo dyes was studied. Mutagenicity of the urine extracts was tested in the Salmonella/mammalian-microsome assay. Results of the mutagenicity assay and gas chromatography analysis of the urine extracts suggested that the azo dyes may decompose and release benzidine. The urinary metabolites of benzidine were more mutagenic than benzidine itself. Azo dyes studied were Direct Deep Black EX and Congo Red, both containing a 4,4'-diazobiphenyl group. (23 Refs)

17. MUTAGENICITY OF 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, 4-NITROSOAZOBENZENE, 4-NITROAZOBENZENE, AND THEIR RING METHOXYLATED DERIVATIVES ON SALMONELLA.

Hashimoto Y, Watanabe HK, Degawa M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):921-929 1981

The mutagenicity of 4-aminoazobenzene (AAB), N-hydroxy-4-aminoazobenzene, 4-nitroazobenzene, and their 2-, 3-, 4'-methoxyl and 2,5-dimethoxyl derivatives, and 2-methoxy-4-nitrosoazobenzene and 3-methoxy-4-nitrosoazobenzene were examined on Salmonella typhimurium TA98 and TA100. The activities of AAB dyes upon S-9 metabolic activation were related to their carcinogenic activities in the rat. The potent carcinogen 3-methoxy-4-aminoazobenzene was a potent mutagen for both tester strains. The moderate or weak carcinogens 4'-methoxy-4-aminoazobenzene and AAB were moderate or weak mutagens for one or both of the tester strains. The noncarcinogens 2-methoxy-4-aminoazobenzene and 2,5-dimethoxy-4-aminoazobenzene were non-mutagenic. In contrast to AAB dyes, N-hydroxy-4-aminoazobenzene dyes showed greater mutagenicity than the mother AAB dyes, without S-9 treatment. 4-Nitroazobenzene dyes and 4-nitrosoazobenzene dyes showed mutagenicity without S-9 treatment, and the activities were related to those of the corresponding N-hydroxy-AAB dyes. All 4-nitroazobenzene dyes were mutagenic in the presence of S-9, suggesting the production of mutagens other than N-hydroxy-AAB dyes by the S-9 treatment. The cytotoxicity of azo dyes to bacteria had no apparent relation to the mutagenic activity of the azo dyes. Incubation of 4-nitroazobenzene dyes with TA100 bacteria yielded N-hydroxy-AAB dyes. The synthesis and properties of new N-hydroxy-AAB dyes, 4-nitroazobenzene dyes and 4-nitrosoazobenzene dyes are described. (Author abstract) (27 Refs)

18. EFFECT OF METHYL SUBSTITUTION ON MUTAGENICITY OF 2-AMINO-3-METHYLIMIDAZO[4,5-F]QUINOLINE, ISOLATED FROM BROILED SARDINE.

Nagao M, Wakabayashi K, Kasai H, Nishimura S, Sugimura T
Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan
Carcinogenesis; 2(11):1147-1149 1981

The compound 2-Amino-3-methylimidazo[4,5-f]quinoline [I] is a potent mutagen isolated from broiled sun-dried sardine. [I] and its seven derivatives, (2 isomers, 1 demethylated derivative and 4 methyl-substituted derivatives), were tested for mutagenicity on Salmonella typhimurium TA98 and TA100 in the presence of S9 mix. 2-Amino-1,4-dimethylimidazo[4,5-f]quinoline was the strongest mutagen of these 8 compounds on TA98, giving 159,000 revertants/nmol (750,000 revertants/ug). The demethylated derivative, 2-aminoimidazo[4,5-f]-quinoline, had very weak mutagenicity, inducing only 55 revertants/nmol (200 revertants/ug). Compounds having a methyl group at position N-1 or N-3 of 2-aminoimidazo[4,5-f]quinoline were strong mutagens. The 1,5-dimethyl-derivative was more mutagenic than the 3,5-dimethyl-derivative. Introduction of a methyl group at position 4 and position 5 enhanced and reduced the mutagenicity, respectively. All the compounds tested were more mutagenic to TA98 than to TA100, but their relative orders of mutagenicity with TA98 and TA100 were the same. (Author abstract) (22 Refs)

19. PULMONARY ADENOMA RESPONSE OF STRAIN A MICE TO SULFONIC ACID DERIVATIVES OF 1-AND 2-NAPHTHYLAMINES.

Theiss JC, Shimkin MB, Weisburger EK
Univ. Texas Health Science Center at Houston, Sch. Public Health, P.O. Box 20186, Houston, TX, 92093
JNCI; 67(6):1299-1302 1981

Various sulfonic acid derivatives of 1-naphthylamine and 2-naphthylamine were tested in inbred A/St (male and female) mice by the pulmonary adenoma bioassay to determine if this class of compounds, used as intermediates in the dye-stuff industry, possesses tumorigenic activity. neither 1-naphthylamine nor the four sulfonic acid derivatives of 1-naphthylamine tested were tumorigenic. However, 2-naphthylamine and two of the three sulfonic acid derivatives of 2-naphthylamine tested produced statistically significant lung tumor responses at comparable doses. These results indicated that this class of compounds should be examined more extensively for carcinogenic activity. (Author abstract) (25 Refs)

20. THE GENETIC ACTIVITY OF DINITROPYRENES IN YEAST: UNUSUAL DOSE RESPONSE CURVES FOR INDUCED MITOTIC GENE CONVERSION.

Wilcox P, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales
Carcinogenesis; 2(11):1201-1205 1981

The compound 1,6-Dinitropyrene (1,6DNP) and 1,8-dinitropyrene (1,8DNP) were tested for their ability to induce mitotic gene conversion at the trp 5 and his 4 loci in the yeast Saccharomyces cerevisiae JD1. Both compounds were shown to be potent inducers of gene conversion in yeast, with 1,6DNP being somewhat more active than 1,8DNP. Unusual dose-response curves were obtained in that toxicity and genetic activity decreased at the higher concentrations examined. This reduction in genetic activity may reflect a decrease in the ability of yeast cells to convert the dinitropyrenes to their mutagenic forms when the concentration of the compounds exceeds a certain level. (Author abstract) (13 Refs)

21. THE SALMONELLA MUTAGENICITY ASSAY ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi A, Bertoncini A, Zadro M
Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy
Arzneim Forsch; 31(12):2140-2142 1981

The antibacterial and antifungal imidazole derivative alpha-(2,4-dichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested for mutagenicity in Salmonella typhimurium in the Ames test. No mutagenicity was detected in strains TA 1535, TA 1537, TA 1538, TA 98, or TA 100 with or without microsomal activation. (5 Refs)

22. MUTAGENICITY STUDIES ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi D, Bertoncini A, Zadro M
Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy
Arzneim Forsch; 31(12):2142-2144 1981

The mutagenicity of alpha-(2,4-didichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested in a forward mutational assay in Schizosaccharomyces pombe and a mitotic gene conversion assay in Saccharomyces cerevisiae. No mutagenicity was detected in either test. In vivo mammalian studies are in progress. (5 Refs)

23. INDUCTION OF SISTER CHROMATID EXCHANGES AND BACTERIAL REVERTANTS BY ORGANIC EXTRACTS OF AIRBORNE PARTICLES.

Lockard JM, Viau CJ, Lee-Stephens C, Caldwell JC, Wojciechowski JP, Enoch HG, Sabharwal PS
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Environ Mutagen; 3(6):671-681 1981

The genotoxicity of organic extracts of airborne particles collected in Lexington, Kentucky was evaluated. In sister chromatid exchange (SCE) assays conducted in human lymphocytes, extracts of all samples induced dose-related increases in number of SCEs. Concentrations of 60 or 80 ug extract/ml caused approximate doubling of background frequency of SCE, to 7.0-9.6 SCE/cell. No metabolic activation was used, indicating that compounds contained in the samples were either direct acting or activated by the lymphocytes. Addition of S9 activation induced negligible increases in number of SCEs for all samples in V79 Chinese hamster fibroblasts. Concentrations of more than 60-80 ug of the extracts were toxic to both human lymphocytes and V79 cells, inhibiting cell division and causing cell lysis. Dose related increases in number of bacterial revertants were induced by all of the organic extracts tested in the Ames assay with both TA98 and TA100. Addition of S9 caused no significant differences in reversion frequencies. (41 Refs)

BINDING OF CARCINOGENS AND THEIR METABOLITES TO MACROMOLECULES

24. METABOLISM AND BINDING OF BENZO(A)PYRENE AND 2-ACETYLAMINOFLUORENE BY SHORT-TERM ORGAN CULTURES OF HUMAN AND RAT BLADDER.

Moore BP, Hicks RM, Knowles MA, Redgrave S
Sch. Pathology, Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England
Cancer Res; 42(2):642-648 1982

The ability of organ cultures of normal human and rat bladder to metabolize the polycyclic hydrocarbon, benzo(a)pyrene (BP), and the arylamine, 2-acetylaminofluorene, has been studied. Cultures were maintained for 0 to 6 days in a chemically defined medium before incubation with [3H]BP (0.3 to 0.5 uM) or 2-[14C]acetylaminofluorene (18 to 25 uM) for 24 hr. Ethyl acetate-soluble and water-soluble metabolites were produced from both compounds by both species. The ethyl acetate extracts from [3 H]BP-treated human cultures contained 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and 3-hydroxybenzo(a)pyrene. Rat bladder cultures produced similar metabolites but in slightly different proportions. Ethyl acetate-soluble products of 2-[14C]acetylaminofluorene from human cultures contained 7-hydroxy-2-acetylaminofluorine, 9-hydroxy-2-acetylaminofluorene, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene. Rat bladder cultures produced similar metabolites, but 2-aminofluorene was found in relatively higher proportion. Hydrolysis by beta-glucuronidase of the water-soluble products produced from both carcinogens gave ethyl acetate-extractable derivatives. These hydrolyzable glucuronide conjugates were relatively more abundant following metabolism of the carcinogens by the rat than by the human cultures. Covalent binding to DNA occurred with [3H]BP in both human (19.7 +-13 pmol/mg DNA) and rat cultures (22.8 +-8.6 pmol/mg DNA). As with other human tissues, considerable variation (50-fold) was observed between individuals. The results demonstrate that both human and rat bladder epithelium can metabolize known potent carcinogens and, in the case of BP, can effect covalent binding between the products of metabolism and the urothelial cell DNA. In theory, carcinogenesis in the urinary bladder could thus be initiated by carcinogens produced or excreted in the urine without the necessity for their prior metabolism elsewhere in the body. (Author abstract) (66 Refs)

25. STUDIES ON THE IN VITRO TRANSFER OF DNA BINDING BENZO[A]PYRENE METABOLITES FROM RAT HEPATOCYTES TO HUMAN FIBROBLASTS.

Nordenskjold M, Svensson SA, Jernstrom B, Moldeus P, Dock L, Soderhall S
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Carcinogenesis; 2(11):1151-1160 1981

The release and reabsorption of benzo[a]pyrene (BP) metabolites were studied in isolated rat hepatocytes incubated with BP. There was a rapid uptake of BP by the hepatocytes which was followed by an excretion of organic as well as water-soluble metabolites. Upon further incubation the BP-dihydrodiols and BP-phenols were reabsorbed by the cells and finally excreted as water-soluble conjugates. The metabolism of BP by the hepatocytes also resulted in the formation and release of reactive intermediates to the incubation medium. The DNA-binding intermediates released from the cells were consistent with trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene-9,10 oxide(s) and 9-hydroxybenzo[a]pyrene-4,5-oxide(s). The BP-metabolites were found to bind to hepatocyte and fibroblast DNA. The degree of DNA binding was estimated as the formation of DNA strand breaks. BP metabolites formed within the hepatocytes and transferred to the fibroblasts were found to induce DNA strand breaks in the latter cells. Addition of DNA to the medium markedly decreased the fraction of single stranded DNA in these cells. Under conditions where the excretion from hepatocytes of BP-phenols and BP-dihydrodiols were increased, the amount of DNA strand breaks in the fibroblasts increased. (Author abstract) (72 Refs)

26. COVALENT BINDING OF BENZO(A)PYRENE TO DNA IN FISH LIVER.

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Biochem Biophys Res Commun; 103(2):780-787 1981

The extent of covalent binding of benzo(a)pyrene (BaP) intermediates to hepatic DNA and protein was determined in English sole exposed po to 3H-BaP. Radioactivity in the liver represented 0.6% of the administered dose at 16 hr. The liver concentration of BaP-derived radioactivity did not change significantly from 16-336 hr after BaP administration; greater than 98% of the total radioactivity in liver was in the form of the organic solvent- and water-soluble metabolites. Detectable binding of BaP intermediates to liver DNA was observed between 6 and 336 hr after BaP exposure. No statistically significant change was observed in the binding values for DNA during the 2 wk exposure; the extent of BaP binding to liver protein did not change significantly over the 2 wk period. The av of all specific activity values for protein (58 +-51) was not significantly different from the av value for DNA (44 +-39). The results indicated that the extent of BaP binding to fish liver DNA is comparable to values reported for mammalian tissues susceptible to polycyclic aromatic hydrocarbon-induced neoplasms; chemical modification of hepatic DNA was observed for at least 2 wk after a single exposure to BaP. (30 Refs)

27. MOLECULAR BIOLOGY OF ENVIRONMENTAL AROMATIC HYDROCARBONS. PROGRESS REPORT, 1 JAN. -31 DEC. 1980.

Weiss SB
Chicago Univ., Chicago, IL
Sci Tech Aerosp Rep; 19(2):240 1981

Three different aspects of hydrocarbon action are investigated: the biochemical effect of benzo(a)pyrene-diol-epoxide on the replication of Simian virus 40; the reaction of benzo(a)pyrene-7,8-diol with viral DNA; and the effect of PAH derivatives on RNA transcription. (Author abstract) (no Refs)

28. STIMULATION OF TRANSFER OF METHYL GROUPS FROM O6-METHYLGUANINE IN DNA TO PROTEIN BY RAT LIVER EXTRACTS IN RESPONSE TO HEPATOTOXINS.

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Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Hershey, PA, 17033
Carcinogenesis; 2(11):1195-1200 1981

An enzymatic activity present in rat liver extracts catalyzes the transfer of methyl groups from O6-methylguanine in DNA to protein. This activity was stimulated by treatment of rats

with thioacetamide, carbon tetrachloride, 1,2-dimethylhydrazine, diethylnitrosamine, dimethylnitrosa mine and by partial hepatectomy but not by treatment with N-methyl-N-nitrosourea or streptozotocin. These results suggest that an enhancement of this activity accompanies the increase in cell division brought about by these agents and is not necessarily a specific response to the presence of alkylated bases in DNA. (Author abstract) (38 Refs)

29. CELLULAR DNA DAMAGE BY NITROSOCIMETIDINE: A COMPARISON WITH N-METHYL-N'-NITROSO-NITROSOGUANIDINE AND X-IRRADIATION.

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Chem Biol Interact; 38(1):87-98 1981

Permanently proliferating lymphoblastoid cell lines (LCLs) and normal unstimulated peripheral blood leukocytes have been used to study the effects of nitrosocimetidine (NC) on cultured human lymphoid cells. The approaches that were used to assess the cells' ability to cope with NC were: (i) determination of cell survival as measured by colony formation in microtiter plates; (ii) quantitation of DNA synthesis and DNA-repair replication by isopyknic sedimentation of DNA density labeled with 5-bromo-2-deoxyuridine (BrdU); (iii) measurement of the induction of alkali labile lesions and strand breaks by NC in 3H-labeled DNA using velocity sedimentation in alkaline sucrose. In summary, treatment with NC was found to inhibit both replicative DNA synthesis and colony formation in LCLs. At the molecular level, NC treatment induced alkali labile lesions in LCL DNA and elicited DNA-repair replication in proliferating LCLs as well as unstimulated lymphocytes. Considered in total, these data indicate that NC is reactive with human DNA in the cellular environment in a manner similar to methylating nitroso compounds which have been shown to be carcinogenic. The significance of these findings will be discussed. (Author abstract) (25 Refs)

30. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

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(c/o Kadlubar) Div. Carcinogenesis, Food and Drug Admin., Environmental Protection Agency, Natl. Center Toxicology Res., Jefferson, AR, 72079
Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

31. AMINO ACID CONJUGATION OF N-HYDROXY-4-AMINOAZOBENZENE DYES: A POSSIBLE ACTIVATION PROCESS OF CARCINOGENIC 4-AMINOAZOBENZENE DYES TO THE ULTIMATE MUTAGENIC OR CARCINOGENIC METABOLITES.

Hashimoto Y, Degawa M, Watanabe HK, Takada M
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Gan; 72(6):937-943 1981

The activation process of N-hydroxy-4-aminoazobenzene (N-HO-AAB) dyes, proximate mutagenic or carcinogenic metabolites of AAB dyes, to the ultimate mutagenic or carcinogenic metabolites was studied by the use of an amino acid conjugation (aminoacylation) system catalyzed by yeast seryl-tRNA synthetase and [3H]ATP. A potent mutagen, N-hydroxy-3-methoxy-AAB (N-OH-3-MeO-AAB), as well as a non-mutagen, N-OH-2-MeO-AAB, were equally susceptible to N-O-serine conjugation. A weak mutagen, N-OH-AAB, and a moderate mutagen, N-OH-2,5-diMeO-AAB, were also susceptible to the aminoacylation, but to a lesser extent than the 2-or 3-methoxyl homologs. In contrast, N-hydroxy-N-methyl-4-aminoazobenzene and a moderate mutagen, N-OH-4'-MeO-AAB, were not susceptible to the aminoacylation. The ability of these N-OH-AAB dyes to bind with nucleic acid after serine conjugation was proportional to the susceptibility of the dyes to serine conjugation. Serine conjugates of N-OH-AAB dyes reacted with poly G, but not with poly A, poly C, or poly U, suggesting that the azo dyes selectively bind with guanine base of nucleic acids. The susceptibility of N-OH-AAB dyes to aminoacylation was compared with the carcinogenic, mutagenic and unscheduled DNA synthesis-inducing activities of these and the mother AAB dyes. (Author abstract) (29 Refs)

32. ABERRANT AND NONRANDOM METHYLATION OF CHROMOSOMAL DNA-BINDING PROTEINS OF COLONIC EPITHELIAL CELLS BY 1,2-DIMETHYLHYDRAZINE.

Boffa LC, Gruss RJ, Allfrey VG
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Cancer Res; 42(2):382-388 1982

The alkylating carcinogen 1,2-dimethylhydrazine (DMH) induces colonic tumors with high incidence. The sites of in vivo modification of target macromolecules were studied using [methyl-3H]DMH. Carcinogen binding to subcellular fractions of colonic epithelial cells was analyzed at time intervals ranging from 10 min to 36 hr, with particular emphasis on the alkylation of nuclear constituents. DMH modifies not only nucleic acids but also histones and other DNA-binding proteins in the target cells. Separation of the 3H-methylated amino acids

showed aberrant methylation patterns after exposure to [3H]DMH, as compared with methylations observed with [methyl-3H]methionine as a natural methyl group donor. DMH-modified histone H1 contained methylated lysine, arginine, and histidine residues not normally found, and other histones had abnormal methylarginine contents. High-mobility-group proteins and other nuclear proteins contained methyllysine residues not normally detected. Proteins known to be associated with template-active and more accessible DNA sequences, such as the high-mobility group proteins and the multiacetylated forms of histones H3 and H4, were preferentially damaged after exposure to [3H]DMH. The result suggests that carcinogen-induced chromosomal damage is not random and may selectively affect proteins in the actively transcribing or replicating genes in the target cells. That damage affects the amino acids most likely to be involved in DNA binding. (Author abstract) (47 Refs)

33. TESTS FOR MUTAGENICITY IN SALMONELLA AND COVALENT BINDING TO DNA AND PROTEIN IN THE RAT OF THE RIOT CONTROL AGENT O-CHLOROBENZYLIDENE MALONONITRILE (CS).

von Daniken A, Friederich U, Lutz WK, Schlatter C
Inst. Toxicology, Swiss Federal Inst. Technology, CH-8603 Schwerzenbach, Switzerland
Arch Toxicol; 49(1):15-27 1981

The aim of this study was to determine whether o-chlorobenzylidene malononitrile (CS) exhibits any genotoxic activity towards Salmonella or mammalian DNA in vivo. CS was synthesized with a [14C]-label at the benzylic carbon atom. It was administered ip at a dose level of 13 mg/kg (1 mCi/kg) to young adult male rats. Liver and kidney DNA was isolated after 8, 25, and 75 hr. The radioactivity was at (liver, 8 and 75 hr) or below (all other samples) the limit of detection of 3 dpm. Therefore, a possible binding of CS to DNA is at least 10(5) times lower than that of the strong hepatocarcinogen aflatoxin B1, and 4,000x lower than that of vinyl chloride. In contrast to this lack of DNA binding, but in agreement with the che mical reactivity of CS, a binding to nuclear proteins could be detected with specific activities ranging between 50 and 121 dpm/mg for liver and between 3 and 41 dpm/mg for kidney. Protein binding could well be responsible for its pronounced cytotoxic effects. CS was also tested in the Ames Salmonella/microsome assay. Strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were used with or without pre-incubation. Only with strain TA 100 and only without pre-incubation, a doubling of the number of revertants was detectable at the highest dose levels used, 1,000 and 2,000 ug CS per plate. With pre-incubation of TA 100 with CS, a slight increase of the number of revertants was seen at 100 and 500 ug per plate, and a subsequent fall below control values at 1,000 ug. A check for the number of surviving bacteria revealed a strong bacteriotoxicity of the higher doses of CS so that the calculated mutation frequencies, ie, the number of revertants per number of surviving bacteria, increased with doses up to 500 ug. This toxicity could be counteracted in part by the addition of increasing amounts of rat liver microsomes. In the view of these results, and taking into account the rare and low exposure of man, it is concluded that CS will not create a risk for the induction of point mutations or of carcinogenic processes mediated by DNA binding. (Author abstract) (26 Refs)

ALTERATION OF MIXED FUNCTION OXIDASES BY CARCINOGENS

34. ACTIVATION OF BENZO(A)PYRENE AND 2-ACETAMIDOFLUORENE TO MUTAGENS BY MICROSOMAL PREPARATIONS FROM DIFFERENT ANIMAL SPECIES: ROLE OF CYTOCHROME P-450 AND P-448.

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Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Xenobiotica; 11(10):701-708 1981

The metabolic activation of benzo(a)pyrene and 2-acetamidofluorene to mutagens was studied with liver microsomal preparations from rat, guinea-pig, hamster and mouse, untreated or pretreated with phenobarbitone or 3-methylcholanthrene. Liver microsomal preparations from all animal species activated benzo(a)pyrene, that from mouse being the most efficient. Similarly, microsomal preparations from guinea-pig, hamster and mouse could activate 2-acetamidofluorene, but that from rat exhibited very weak activity. Activation of benzo(a)pyrene into mutagenic intermediates by liver microsomal preparations was increased for all animals except mouse by pretreatment with 3-methylcholanthrene. In contrast, pretreatment with phenobarbitone decreased the activation by microsomal preparations from all species. Activation of 2-acetamidofluorene by liver microsomal preparations from rat and guinea-pig, but not mouse and hamster, was increased by pretreatment of the animals with phenobarbitone. Pretreatment with 3-methylcholanthrene decreased the activation of this carcinogen by microsomal preparations from all species. The m etabolic activation of benzo(a)pyrene is catalyzed by cytochrome P-448 but not cytochrome P-450. The activation of 2-acetamidofluorene to mutagens may involve, in addition to the mixed-function oxidases, other microsomal enzyme systems. (Author abstract) (29 Refs)

35. STRUCTURAL GENE PRODUCTS OF THE AH LOCUS. EVIDENCE FOR MANY UNIQUE P-450-MEDIATED MONOOXYGENASE ACTIVITIES RECONSTITUTED FROM 3-METHYLCHOLANTHRENE-TREATED C57BL/6N MOUSE LIVER MICROSOMES.

Lang MA, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12058-12067 1981

Cytochrome P-450 from cholate-solubilized liver microsomes prepared from 3-methylcholanthrene-treated genetically 'responsive' C57BL/6N mice (Ahb/Ahb) was partially purified by aminooctyl-Sepharose 4B column chromatography with an elution buffer that included Emulgen 911, followed by hydroxylapatite column chromatography. The P-450 was separated into 16 fractions: 15 fractions principally associated with the Ahb allele and induction by 3-methylcholanthrene and 1 fraction not associated with the Ahb allele, ie predominantly constitutive form(s) of P-450. The metabolism of benzo[a]pyrene, 7-ethoxycoumarin, biphenyl, ethoxyresorufin, acetanilide, 2-acetylaminofluorene, phenacetin, estradiol-17beta, and testosterone was investigated. With these nine substrates, we examined the rates of formation of 17 products, ie 17 P-450-mediated reconstituted monooxygenase 'activities,' in each of the 16 fractions. Differing reductase/cytochrome and lipid/cytochrome requirements were observed for each activity; the reasons

for these empirical differences are not known. By two-factor analysis of variance, our data for 17 catalytic activities can be explained by a minimum of 19 unique groups of monooxygenase activities: 12 induced by 3-methylcholanthrene and 7 control (endogenous). At least one of these distinctly different 3-methylcholanthrene-induced groups and at least one of these constitutive groups is associated with a marked blue spectral shift (approx 2.0 nm) in the Soret peak of the reduced hemoprotein-CO complex, suggesting multiple forms of inducible and control 'P-448.' Almost every reconstituted monooxygenase activity therefore appears to be unique and probably represents the aggregate activity from numerous forms of P-450. (Author abstract) (43 Refs)

36. PRESENCE OF BENZO[A]PYRENE METABOLIZING ACTIVITIES IN ISOLATED RAT LIVER NUCLEOLI.

Lafarge-Frayssinet C, Alexandrov K, Rimbaut C, Dansette PM, Mousset S, Frayssinet C
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Carcinogenesis; 2(11):1189-1193 1981

A benzo[a]pyrene (B[a]P) hydroxylase activity and epoxide hydrolase (EH) activity have been found in rat liver nucleoli obtained from untreated (C) and 3-methylcholanthrene (3-MC) pretreated rats. A comparison of the enzyme activities was made in rat nuclei and nucleoli. Light and electron microscopic observations of nucleolar preparations did not reveal significant contamination either by intact nuclei or by nuclear membranes, and glucose 6-phosphatase, a marker of microsomal activity, was not detected in our nucleolar preparations. NADPH cytochrome c-reductase could be measured in C and 3-MC nuclei and very low but detectable activity was found in the nucleoli. Nucleolar preparations revealed significant hydroxylating activity, which was inducible by 3-MC in nuclei but not in nucleoli. The presence of EH in nucleoli was demonstrated with phenanthrene 9,10-oxide and B[a]P 4,5-oxide, but the nucleolar activities were lower than those obtained using intact nuclei. The addition of 1,1,1-trichloropropene 2,3-oxide completely inhibited EH activity. Furthermore the presence of covalently-bound metabolites of B[a]P formed in isolated nucleoli was demonstrated by cytofluoromicroscopy. (Author abstract) (30 Refs)

37. GENETIC EVIDENCE FOR MANY UNIQUE LIVER MICROSOMAL P-450-MEDIATED MONOOXYGENASE ACTIVITIES IN HETEROGENEIC STOCK MICE.

Lang MA, Gielen JE, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12068-12075 1981

Total cytochrome P-450 content, the Soret maximum of the reduced P-450-CO complex, NADPH-cytochrome c reductase activity, and 20 monooxygenase activities were determined in liver microsomes from each of 12 individual Heterogeneic Stock (HS) mice at varying times after 3-methylcholanthrene treatment. The choice of genetically very heterogeneous mice and the possibility of different turnover rates (synthesis/degradation) during the 3-methylcholanthrene induction process provided us with a strong likelihood of detecting differences in drug-metabolizing enzyme activities. Such diversity would also be expected among the human population. The substrates included benzo[a]pyrene, ethoxyresorufin, biphenyl, p-nitroanisole, 2-acetylaminofluorene, 7-ethoxycoumarin, zoxazolamine, estradiol-17beta, testosterone, progesterone, pregnenolone, dehydroepiandrosterone, and aldrin. By two-factor analysis of variance, 18 unique liver microsomal monooxygenase activities appear to be distinctly different from one another, out of the 20 activities chosen for study. Ethoxyresorufin O-deethylase activity is significantly correlated ($p = 0.11$) with aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Dehydroepiandrosterone 16alpha-hydroxylase activity correlates well with the testosterone ($p = 0.33$), progesterone ($p = 0.16$), and pregnenolone ($p = 0.11$) 16alpha-hydroxylases. Testosterone 16alpha-hydroxylase, progesterone 16alp ha-hydroxylase, and pregnenolone 16alpha-hydroxylase activities, on the other hand, are all significantly (p less than 0.001) different from one another. These data with intact microsomes illustrate the complexity of the problem with multiple P-450-mediated monooxygenases. Almost every activity therefore appears to be unique and probably reflects the aggregate contribution from numerous forms of P-450. (Author abstract) (33 Refs)

ALTERATION OF OTHER CARCINOGEN-METABOLIZING ENZYMES BY CARCINOGENS

38. SIALIC ACID METABOLISM IN NUTRITIONALLY MODULATED MAMMARY GLAND CARCINOGENESIS.

Fox OF, Kishore GS, Carubelli R
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Cell Mol Biol; 27(5):473-482 1981

The activities of CMP-N-acetylneuraminic acid synthetase, sialyltransferase and neuraminidase were investigated in female Sprague-Dawley rats with mammary adenocarcinomas induced by oral administration of 7,12-dimethylbenz[a]anthracene. The carcinogenic process was modulated by the levels and degree of unsaturation of the dietary lipids in the presence and in the absence of dietary antioxidants. The activities of the biosynthetic enzymes responsible for the activation and transfer of sialic acids, ie CMP-N-acetylneuraminic acid synthetase and sialyltransferase were higher in tumors than in control mammary glands. The cytosolic and membrane-bound neuraminidases, on the other hand, were higher in control tissue than in tumors. In the low-fat dietary group, which had the lowest rate of tumor incidence, a tocopherol effect on sialic acid metabolism was detected; rats fed low-fat diet supplemented with alpha-tocopherol exhibited the highest levels of control mammary gland sialyltransferase activity, whereas tocopherol deficiency was accompanied by a loss of the tumor-dependent enhancement of CMP-N-acetylneuraminic acid synthetase. The enzyme profiles in the livers of control and tumor-bearing rats, although less well defined, showed some of the general trends observed in mammary tissues. (Author abstract) (21 Refs)

39. PHOSPHOLIPASE ACTIVITY IN SKIN AFTER APPLICATION OF PHORBOL ESTERS AND 3-METHYLCHOLANTHRENE.

Bresnick E, Bailey G, Bonney RJ, Wightman P
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Carcinogenesis; 2(11):1119-1122 1981

Topical administration of the promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), is accompanied by an increased incorporation of [3H]arachidonic acid into mouse

skin and a very significant activation of epidermal cell membrane phospholipase A2 without affecting intracellular acid phospholipase. Similar enhancement in epidermal cell phospholipase A2 was observed after application of phorbol-12,13-didecanoate or 3-methyl-cholanthrene to mouse skin. A small but significant increase in phospholipase A2 activity is also seen after application of the nonpromoter irritant, acetic acid. The elevated levels of the prostaglandins observed in mouse skin after topical application of promoters are probably triggered by the activation of this membrane enzyme. (Author abstract) (25 Refs)

40. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

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Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AIDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AIDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare the effects of a variety of tumor induction protocols on the AIDH phenotype. No change in the AIDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen or promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AIDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AIDH phenotype. No correlation exists between tumor size and the degree of deviation of the AIDH phenotype from normal. Nor is there any correlation between the degree of AIDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AIDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AIDH phenotype. (Author abstract) (22 Refs)

41. EFFECT OF INDOLE ON N-NITROSODIMETHYLAMINE DEMETHYLASE IN RATS TREATED WITH CARBON TETRACHLORIDE.

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Food Cosmet Toxicol; 19(6):717-721 1981

Carbon tetrachloride (CCl_4) significantly decreased N-nitrosodimethylamine demethylase activity in Fisher rats in a dose-dependent fashion. After indole treatment, however, demethylase a ctivity was increased, reaching a maximum after 6-12 days of indole feeding. The inhibitory action of CCl_4 could be modified by indole feeding. (28 Refs)

42. INHIBITION OF ENZYMATIC DNA METHYLATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN HUMAN RAJI LYMPHOBLAST-LIKE CELLS.

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Int J Biochem; 13(12):1225-1232 1981

A single treatment of the human Raji lymphoblast-like cell line with N-methyl-N'-nitro-N-nitrosoguanidine caused undermethylation of DNA which persisted in cell cycles following treatment. A possible relationship of such demethylation with aberrant phenotypic expression is discussed. (36 Refs)

43. ELEVATED LEVELS OF ORNITHINE DECARBOXYLASE AND POLYAMINES IN THE KIDNEYS OF ESTRADIOL-TREATED MALE HAMSTERS.

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Carcinogenesis; 2(11):1207-1211 1981

The effects of 17 beta-estradiol (E2) on the levels of ornithine decarboxylase (ODC), S-adenosylmethionine decarboxylase (SAMDC), and of the polyamines putrescine, spermidine and spermine in the kidneys of castrated male hamsters were determined. The ip injection of E2 into male hamsters led to renal ODC levels three times above the control levels 6-12 hr after treatment. Similarly, the renal ODC levels in hamsters treated with chronic doses of E2 for 60-180 days were 1.5-1.9 times the corresponding enzyme levels in control, sham-operated animals. With a series of estrogen analogues, there was a direct correlation between the rise in renal ODC in vivo and the binding to renal estradiol receptor sites in vitro. The hamster kidney levels of the polyamines putrescine, spermidine and spermine all declined during the 180-day experimental period. A single ip injection of E2 led to a 70% increase in renal SAMDC activity 12 hr after treatment. However, the administration of E2 for 180-270 days was without effect on the normal age-dependent decline in SAMDC levels noted in kidneys. These results indicate that, like other carcinogens and promoters, E2 increases the levels of ODC and of polyamines in its target tissue and that the rise in ODC is mediated by a specific estradiol-binding protein. (Author abstract) (30 Refs)

44. DIMINUTION OF MOUSE EPIDERMAL SUPEROXIDE DISMUTASE AND CATALASE ACTIVITIES BY TUMOR PROMOTERS.

Solanki V, Rana RS, Slaga TJ
Biology Div., Cancer and Toxicology Program, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 2(11):1141-1146 1981

The effects of phorbol ester tumor promoters and related compounds on superoxide dismutase (SOD) and catalase were examined. The treatment of adult mouse skin with 2 ug 12-O-tetradecanoylpho rbol-13-acetate (TPA) resulted in a sustained decrease in the basal levels of both SOD and catalase activities in the epidermis. A decline in SOD activity occurred within 3 hr after application and the maximum effect was seen at 16-17 hr. The decrease in SOD activity was always accompanied by a similar decline in the epidermal catalase activity. The alterations in both enzymes occurred against a high background of enhanced protein synthesis which indicates that the effect of TPA is selective for SOD and catalase. Other tumor promoters such as phorbol 12,13-dibutyrate and the non-phorbol tumor

promoter anthraline also lowered the activities of both the enzymes. Mezerein, a resiniferonol derivative with weak promoting activity but a potent Stage-II promoter, appeared to be more potent than TPA in lowering the basal levels. These results indicate that damage which favors neoplastic progression could occur in TPA-treated mouse skin due to the accumulation of free radicals resulting from low levels of SOD and catalase activity. In addition, the TPA-caused decrease in the levels of SOD and catalase was not prevented by either retinoic acid, fluocinolone acetonide, tosyl amino-2-phenylethyl chloromethyl ketone, or butylated hydroxytoluene, suggesting that inhibition of tumor promotion by these agents is not mediated through alterations in the levels of enzymatic activities which decrease free radical concentrations. (Author abstract) (29 Refs)

45. DELAYED INDUCTION OF ORNITHINE DECARBOXYLASE IN MOUSE SKIN AFTER IRRADIATION WITH BETA-RAYS.

Fujiki H, Mori M, Tanooka H
National Cancer Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Cancer Lett; 15(1):15-17 1982

Delayed increase of ornithine decarboxylase (ODC) activity in mouse skin after irradiation with 90Sr-90Y beta rays was studied. Female 8-wk-old CD-1 mice were used in all experiments. The hair on their backs was clipped and further removed 2-3 days before irradiation. The shaved area was irradiated with beta-rays from the 90Sr-90Y source plated on 2-cm diameter metal disk for 13 min at a dose of 230 rad/min on the surface of the skin. Total irradiation dose was 3 kilorad. ODC activity for untreated mice was 0.01 nanomole CO2/30 min/mg protein. The ODC activity remained at the control level until day 14 and then increased to max on about day 17; ODC activity decreased after that, reaching the starting level on about day 20. The visible acute skin reaction was also delayed, reaching max on day 16-20. Beta rays differ from tumor promoters and carcinogens in causing delayed ODC induction. Results indicate that beta rays induce a phenotypic change associated with tumor promotion. (7 Refs)

REVIEWS AND OTHER RELEVANT STUDIES

46. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carcinogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

47. TYPES OF MATERIALS AND TESTS (MEETING ABSTRACT).

Bridges JW, Hubbard SA
Robens Institute of Industrial and Environmental Health and Safety, University of Surrey Guildford, GU2 5XH, England
Mutagenicity Testing, October 12, 1981, London, England, Royal Society of Chemistry; 1981

Many carcinogens exert their effects indirectly through the formation of reactive metabolites. The formation of these reactive metabolites is brought about by the drug metabolizing enzymes of the cell, a group of enzymes whose primary role appears to be the conversion of lipid soluble substances to water soluble excretable products. In many mutagenicity tests a 9,000 xg fraction of rat liver homogenate (S9) is added to mimic the in vivo ability of tissues to form these reactive metabolites. The quantity and quality of S9 fraction which is added may cause large variations in the observed mutagenic response. The degree of mutagenicity is also affected greatly by the previous chemical exposure and diet of the rats from which the S9 fraction is derived. A number of other factors are also very imporant: a) The form in which the chemical is presented to the biological system. Particular problems are often experienced in assessing the mutagenicity of insoluble particulates, intensely colored materials, volatile substances and compounds which bind avidly to plastic. b) The medium in which the metabolizing and mutagenic response systems are suspended and the nature of any cellular membranes between them. This influences the passage of any reactive metabolites formed into the response system. c) The nature of the response system itself. No single set of experimental conditions is ideal for assessing the mutagenicity of all chemicals, rather the experimental conditions should be selected bearing in mind the physical and chemical properties of the material which is being tested. (no Refs)

48. TOXIC DRUG EFFECTS ASSOCIATED WITH OXYGEN METABOLISM: REDOX CYCLING AND LIPID PEROXIDATION.

Kappus H, Sies H
Inst. Umweltbygiene, Univ. Dusseldorf, Moorenstrasse 5, D-4000 Dusseldorf, W. Germany
Experientia; 37(12):1233-1241 1981

Various endogenous and exogenous compounds exert cytotoxic effects via oxygen reduction. In general, these are reduced by intracellular enzymes (reductases of various kinds) in one-electron transfer reactions, before they in turn reduce O2 to O2-, the superoxide anion radical. Thus, a cycle is formed of O2 uptake at the expense of cellular reducing equivalents, notably NADPH, generating further active oxygen species. Structures capable of 'redox cycling' include catechols and other quinone compounds, iron chelates, and aromatic nitro compounds. Several anticancer agents, and also some mutagens, operate on this principle, and their toxic effects may be explained by redox cycling. The particular importance of hypoxic conditions for deleterious O2 effects is given by the con-

comitant flux through reductive as well as oxidative pathways. Toxic effects include membrane damage resulting from peroxidative reactions of polyunsaturated fatty acids (lipid peroxidation), as well as the attack of reactive oxygen species on proteins (enzymes) and nucleic acids; thus O2 metabolism is linked to carcinogenicity and mutagenicity. Lipid peroxidation is also induced by various halogenated compounds such as carbon tetrachloride. Again, hypoxic conditions are particularly critical because, on the one hand, metabolic activation leading to the free radical is enhanced and, on the other hand, oxygen required for the maintenance of lipid peroxidation is still available. Powerful antioxidant systems of the cell maintain low steady state concentrations of oxygen metabolites, and toxic effects may, in part, also be explained by the constant drain of reducing equivalents resulting from redox cycling. (Author abstract) (137 Refs)

49. EFFECTS OF STRUCTURE ON THE CARCINOGENIC BEHAVIOR OF NITROSAMINES.

Wishnok JS
Dept. Nutrition and Food Sciences, Massachusetts Inst. Technology, Cambridge, MA, 02139
ACS Symp Ser; 174(0):77-87 1981

Small, closely-related series of nitrosamines have been examined and a quantitat ive structure-activity model (QSM) based on molecular descriptors (physicochemical, geometrical, topological, and electronic) has been developed. The final form of QSM can be interpreted in terms of the proposed mechanisms of action or of modified aspects of these mechanisms. Nitrosamines are highly sensitive towards one or a few target organs. Test compounds included 13 dialkylnitrosamines which induced tumors in the liver or in the lung or esophagus. All test compounds were administered at equal daily doses. Relative properties of compounds reflect then only the differences in the molecular structure of the test substances. The model for organ selectivity requires terms for the parent nitrosamine as well as for the hypothesized metabolites while the model for potency variations contains terms only for the unmetabolized parent compound. (29 Refs)

50. HISTOLOGICAL EVIDENCE OF 'ESTROGENIC PROPERTIES' OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Valero D, Drouhault R, Vanhems E, Bousquet J, Blanquet P
Unite 53, I.N.S.E.R.M., Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France
Cell Mol Biol; 27(2/3):263-269 1981

DMBA (7,12-dimethylbenz(a)anthracene) and estradiol provoke in rat pituitaries an increase of prolactin cells number and of hormone synthesis. It is a transitory effect. Both enhance equally G6PD activity, this enzyme acting for an end product of a functional estradiol receptor. This increased reactivity persists during mammary tumor growth. These data added to previously published results, support the hypothesis that carcinogen would act in part by 'estrogen-mimetic' properties. (Author abstract) (25 Refs) (In FRE)

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1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

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2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

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4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
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Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
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Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
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7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
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Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

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10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
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METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 277 09
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
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